Bacterial quorum sensing as a networked decision system

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***Abstract*—Quorum sensing plays a significant role in infection, biofilm production and potentially can impact the design of microbial fuel cells in the future. Herein, a production of public-goods interpretation is employed to introduce a novel optimization-based model for bacterial quorum sensing. In this model, each bacterium cell act as a decision-maker seeking to maximize a pay-off function under the uncertainty on the concentration of the colony population. First, the design of a socially optimal strategy profile is considered, where all the cells employ the same threshold strategy. Second, the probability of not activating while the quorum is being formed is analyzed; this phenomenon is known in the literature as *cheating*. Lastly, preliminary results are presented that establish a connection between the new decision-making model with experimental data.**

I. Introduction

Bacteria are simple unicellular organisms and one of the earliest forms of life on Earth. Despite their apparent simplicity, bacteria use a sophisticated communication system to coordinate global behavior known as *quorum sensing* [1], [2]. Understanding and controlling this communication mechanism may have huge impact on new ways to prevent undesirable bacterial infections [3], lead to new nano-fabrication methods, and the design of nano-communication networks [4]. Since bacteria have existed for billions of years, it is likely that quorum sensing systems may have evolved and adapted to robustly achieve optimal performance of the colony, which led to the survival of the species through time. We investigate quorum sensing systems under an optimization paradigm where the cells act as *decision makers* as in [5].

A simplified version of a quorum sensing mechanism is shown in Figs. 1 and 2 and can be succinctly described as follows: each cell in a bacterial colony is able to produce an enzyme responsible for special effects, named *exofactors*. Typical examples of exofactors are fluorescence, virulence and formation of biofilm. Each of these have its own role in the overall fitness of the colony either directly or indirectly via symbiosis with a host organism. However, this *public-benefit* can only be experienced if enough cells decide to activate simultaneously. In other words, the benefit from expressing an exofactor is only reaped if a *quorum* is established, e.g., if at least half of the population activates. Furthermore, this public-benefit scales with the concentration of cells in the colony [6], [7], which is unknown to the individual cells and cannot be directly observed. In order to sense the environment each cell in colony produces signaling molecules named *auto-inducers*, which are released and propagate in the environment. The overall concentration of auto-inducers is proportional to the density of the colony. Finally, each cell is capable of sensing the environment by means of proteins called *receptors* that bind to the auto-inducers forming *complexes*. Once the number of complexes exceeds a certain threshold, the cell activates the production of the exofactor. Notice that with this sensing mechanism, each cell never has a perfect observation of the true density of the colony, and can only form a crude estimate.

We model quorum sensing as a distributed decision making mechanism consisting of multiple agents making partial observations about the state of the environment. Based on its observation, each agent makes a binary decision to activate (or not) the production of a costly public good. The goal of the agents in our model is to optimize a pay-off function that consists of a *public benefit* and a *local activation cost*. Interestingly, this optimization-based model coincides with the following: based on its observation each cell forms a local estimate of the population $\hat{X}_i$. Based on this estimate, it chooses the action to activate or not the production of exofactor. The model proposed here captures the essence of the underlying decision-making mechanism that takes place in quorum sensing, is simple enough in order to allow for mathematical analysis, optimization and calibration of key parameters.

The key contributions of our work are to:

- Provide a new networked decision theoretic model of quorum sensing, where the agents optimize the overall fitness of the colony.
- Provide a numerical analysis and threshold optimization for several combination of parameters in the model.
- Calibrate our model with data collected from quorum sensing experiments performed in laboratory.

This paper is organized as follows. Section II describes the networked decision-making model for quorum sensing. Section III provides the analysis of the system. In Section IV, we employ experimental data to estimate the values of our system parameters and perform model calibration. Section V concludes the paper.

A. Related literature

Quorum sensing was discovered by Nealson et al. and first reported in [8], spurring a very diverse body of literature. Most of the mathematical models of quorum sensing seek to capture the dynamical behavior of the concentration of the different quantities over time. The work of Michelusi et al. [9] uses a queuing based model to study the evolution of quorum sensing systems. Popat et al. [10] investigate the interaction of two different coexisting colonies that use quorum sensing

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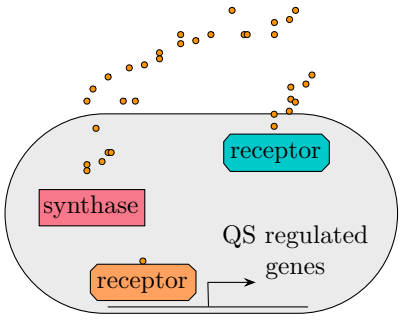

Fig. 1. Basic quorum sensing system of a bacterium cell. The cell releases auto-inducers at a rate λ and receive them at a rate λX, where X is the unknown density of the bacterial colony. Once enough auto-inducers are received, the cell expresses the gene to the corresponding exofactor.

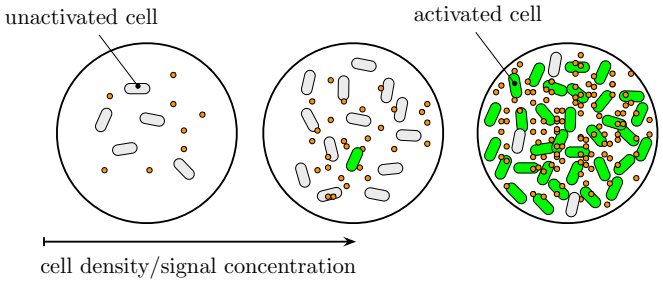

Fig. 2. The activation of cells depends on the concentration of auto-inducers in the environment, which is proportional to the density of cells.

to coordinate behavior. Game theoretic models have also been used to model quorum sensing and study social interactions among different colonies [11]. More recently, Michelusi and Mitra have studied quorum sensing from an estimation theoretic point of view [12], [13]. Among the many mathematical models available in the literature, our work is closest to the model of Heilmann et al. [14]. However, our work focuses on a static optimization problem under uncertainty, rather than the deterministic dynamic model in [14]. This uncertainty in the population concentration of bacteria has also been explored in a recent paper by Noel et al. [15], but for a different model than the one considered here.

Networked decision systems consist of multiple agents, who make local measurements, communicate over a shared network and make decisions with the goal of achieving a common or individual objectives [16]. We argue that this framework is appropriate for modeling quorum sensing systems similar to the approach taken by Einolghozati et al. in [17], where the goal is to coordinate a global behavior based on local measurements and under uncertainty on the density population. 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 general quorum sensing systems in this framework, we need to understand the simpler case with a single colony.

II. The Model

In this section we describe the Bayesian decision-making framework used in this paper. We assume that there is a certain number of cells per unit of volume in the colony and that each of these cells act as a decision maker.

A. State-of-the-world

From the perspective of an individual cell, the most fundamental unknown quantity in a quorum sensing system is the concentration of cells in the colony, also known as the population density. The concentration is defined as the number of cells per unit volume occupied by the bacterial colony and corresponds to the *state-of-the-world* in the Bayesian decision problem. The population density is represented by a nonnegative random variable X, with a known continuous probability density function f_X supported on $[0, \infty)$, i.e.,

$$X \sim f_X(x). \tag{1}$$

In this paper we will assume that the population density is Gamma distributed with parameters $k, \theta > 0$, i.e.,

$$f_X(x) = \frac{x^{\kappa-1} \cdot \exp\left(-\frac{x}{\theta}\right)}{\theta^{\kappa} \cdot \Gamma(k)}, \quad x \geq 0. \tag{2}$$

For this distribution, $\mathbf{E}[X] = \kappa\theta$ and $\mathbf{V}[X] = \kappa\theta^2$.

Remark 1: Our choice of modeling the concentration of bacteria as a Gamma random variable comes from the fact that this 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 analysis when paired with the Poisson observation model that we will introduce next. Finally, this prior distribution has been previously used for Bayesian estimation of bacterial concentration in a substance from microbial count data in [19].

B. Measurements

The concentration is unknown to each cell and is not directly observed by any of the cells in the colony. In quorum sensing, a cell probes the concentration of bacteria in the surrounding environment by indirectly measuring the concentration of *auto-inducer* molecules. Each cell in the colony secretes auto-inducers in the environment at a rate $\lambda > 0$. The global concentration of auto-inducers is proportional to the number of cells in the colony. Auto-inducers are discrete entities, which are produced by proteins named *synthases*. During the signaling process, the auto-inducers in the environment bind to proteins called *receptors* to form *complexes*. We model that the number of auto-inducers received and bound to receptors is distributed according to a Poisson probability mass function, whose arrival rate is proportional to the concentration of cells in the colony X.

Let the observation of the i-th cell in the colony be represented by Y_i. Therefore, given $X = x$, we have

$$Y_i \sim \mathcal{P}(\lambda x), \quad i \in \{1, 2, \cdots, \lfloor x \cdot \text{vol} \rfloor\}, \tag{3}$$

where vol is the volume occupied by the colony. Therefore,

$$\mathbf{P}(Y_i = k \mid X = x) = \frac{(\lambda x)^k}{k!} e^{-\lambda x}, \quad k = 0, 1, 2, \cdots \tag{4}$$

Finally, for the sake of tractability of our model, we assume that conditioned on $X = x$, the measurements Y_i, $i \in \{1, \cdots, \lfloor x \cdot \text{vol} \rfloor\}$ are mutually independent. Without loss of generality, for the remainder of the paper we will assume that $\text{vol} = 1$.

C. Actions

Once the measurements are made, the cells use a *strategy* to decide whether to engage or not in the production of the *exofactor*, which may correspond to a virulence attack, biofilm formation, fluorescence, among others. The action of the i-th cell is denoted by a binary random variable $A_i \in \{0, 1\}$, where

$$A_i = \begin{cases} 1, & \text{if the exofactor is produced} \\ 0, & \text{if the cell remains idle.} \end{cases} \tag{5}$$

The decision of the i-th bacteria is taken according to a *strategy* denoted by $\gamma_i : \mathbb{Z}_{\geq 0} \to [0, 1]$, where

$$\mathbf{P}(A_i = 1 \mid Y_i = y) \stackrel{\text{def}}{=} \gamma_i(y). \tag{6}$$

The collection of strategies $\boldsymbol{\gamma} \stackrel{\text{def}}{=} \{\gamma_1, \cdots, \gamma_{\lfloor x \rfloor}\}$ is called a *strategy profile*. A particular class of strategies that is known to play a fundamental role in quorum sensing systems is the the class of *threshold strategies*. A threshold strategy is a deterministic function parametrized by a single nonnegative real number α_i, and is defined as follows:

$$\gamma_i(y) \stackrel{\text{def}}{=} \mathbf{1}(y \geq \alpha_i). \tag{7}$$

The action of producing the exofactor, when taken according to a threshold policy, implies that the cell uses the number of received auto-inducers as a proxy for the concentration of bacteria in the colony.

D. Pay-off

Unlike the production of auto-inducers, which are energetically cheap molecules, exofactors are costly. Moreover, the production of a particular exofactor only pays-off once a sufficient number of cells in the colony decide to activate its production.

Definition 1 (Quorum size): Let $\tau \in [0, 1]$. For a colony with N cells, a quorum of size τN is established if at least τN cells decide to activate, i.e.,

$$\sum_{i=1}^{N} a_i \geq \tau N. \tag{8}$$

We propose an individual pay-off function whose structure consists of two terms: a public benefit term and a local activation cost as follows

$$\mathcal{U}_i(a_i, a_{-i}, x) \stackrel{\text{def}}{=} \underbrace{\tau \lfloor x \rfloor \cdot \mathbf{1}\left(\sum_{i=1}^{\lfloor x \rfloor} a_i \geq \tau \lfloor x \rfloor\right)}_{\text{public benefit per cell}} - \overbrace{c \cdot a_i}^{\text{local cost}}, \tag{9}$$

where a_i denotes the action of the i-th cell, and a_{-i} denotes the vector of actions of all the cells in the colony with the exception of the i-th cell. We will elaborate more on each of these terms.

1) Local cost: The local activation cost corresponds to the energetic cost for producing the exofactor. This term is equal to zero if the cell decides not to activate and is equal to a nonnegative constant c otherwise.

2) Public benefit: For a colony of size $\lfloor x \rfloor$, the public benefit is equal to zero unless a quorum of size $\tau \lfloor x \rfloor$ is formed. If the quorum is established, the public benefit equals the quorum size. The interpretation behind this benefit function is that a minimum number of cells needs to be active before the colony starts to enjoy the public benefit. Since it is easier to reach the quorum for lower values of τ, we assume that the overall fitness of the colony is proportional to τ. Once it is nonzero, the public benefit is constant in the actions of the agents. Notice that since x is not known *a priori*, the cells do not know exactly how much public benefit will be produced by their actions. Finally, we remark that the true values for c and τ for specific bacterial colonies are presently unknown.

E. Threshold optimization problem

In the remainder of the paper we will assume that all the cells in the colony will use threshold strategies parametrized by the same parameter α, i.e.,

$$\alpha_i = \alpha, \quad i \in \{1, \cdots, \lfloor x \rfloor\}. \tag{10}$$

We are now ready to state the main optimization problem considered in this paper.

Problem 1: Given the parameters $\kappa, \theta, \lambda > 0$, and $c \geq 0$, find α that maximizes the function $\mathcal{J}_i$ given by

$$\mathcal{J}_i(\alpha) \stackrel{\text{def}}{=} \mathbf{E}\Big[\mathcal{U}_i(A_i, A_{-i}, X)\Big] = \mathcal{J}(\alpha). \tag{11}$$

Remark 2: The solution of Problem 1 can be understood as the socially optimal threshold for the colony. It is unlikely that this solution, when it exists, forms a Nash-equilibrium strategy. However, this solution concept is a starting point for analyzing the more general problem formulation in which a Nash-equilibrium is sought.

III. Analysis

We start by computing the conditional probability of activation of a single cell (local activation). Let $i \in \{0, \cdots, \lfloor X \rfloor\}$. Given $X = x$ and assuming that every cell uses the same threshold $\alpha \in \mathbb{R}_{\geq 0}$, the probability of local activation is defined as

$$p(x; \alpha, \lambda) \stackrel{\text{def}}{=} \mathbf{P}(A_i = 1 \mid X = x) \tag{12}$$

and is computed as follows

$$p(x; \alpha, \lambda) = \mathbf{P}(Y_i \geq \alpha \mid X = x) = \sum_{k=\lceil \alpha \rceil}^{\infty} \frac{(\lambda x)^k}{k!} e^{-\lambda x}. \tag{13}$$

The next step is to compute the conditional probability of global activation. Let $L(X)$ denote the total number of activated cells in a colony of density X, i.e.,

$$L(X) \stackrel{\text{def}}{=} \sum_{i=1}^{\lfloor X \rfloor} A_i. \tag{14}$$

Conditioned on $X = x$ and for given α and λ, each A_i is a Bernoulli random variable with parameter $p(x;\alpha,\lambda)$. Since the observations Y_i, $i \in \{1 \cdots, \lfloor x \rfloor\}$ are conditionally independent given $X = x$ and that each decision variable A_i is only a function of Y_i, the random variable $L(x)$ has a Binomial distribution with parameters $\lfloor x \rfloor$ and $p(x;\alpha,\lambda)$. Therefore,

$$\begin{aligned}\mathbf{P}\big(L(X) = \ell \mid X = x\big) \\ = \binom{\lfloor x \rfloor}{\ell} \big(p(x;\alpha,\lambda)\big)^{\ell} \big(1 - p(x;\alpha,\lambda)\big)^{n-\ell}.\end{aligned} \tag{15}$$

Using these two probabilities we can express the objective function as follows.

Proposition 1: Consider Problem 1. The pay-off function in Eq. (11) can be explicitly computed according to

$$\begin{aligned}\mathcal{J}(\alpha) = \int_0^{\infty} \Bigg[\tau \lfloor x \rfloor \sum_{\ell = \lceil \tau \lfloor x \rfloor \rceil}^{\lfloor x \rfloor} \binom{\lfloor x \rfloor}{\ell} \big(p(x;\alpha,\lambda)\big)^{\ell} \big(1 - p(x;\alpha,\lambda)\big)^{n-\ell} \\ - c \cdot p(x;\alpha,\lambda) \Bigg] f_X(x) dx.\end{aligned} \tag{16}$$

Proof: The result follows from iterated expectations first conditioning on X, and using Eqs. (13) and (15). ∎

Remark 3: 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 $p(x;\lambda,\alpha)$, which is not smooth in α, can be well approximated by a *regularized incomplete Gamma function*. This approximation leads to a differentiable objective function.

A. Pay-off function and optimal thresholds

In order to illustrate the general shape of the pay-off functions, consider the following set of parameters: Let $\theta = 50$ and $\kappa = 2$, which implies that the average concentration of cells in the colony is $\bar{X} = 100$ cells per unit volume; $\lambda = 1$, and activation cost $c = 50$. For different values of the quorum ratio τ, Fig. 3 shows the pay-off function. For these choices of parameters, $\mathcal{J}(\alpha)$ is unimodal and has a unique maximizer, which are displayed in Table I.

Figure 4 shows the dependency of the pay-off function with the local activation cost c. Here, we assume that $\theta = 50$, $\kappa = 2$, $\lambda = 1$, and $\tau = 0.75$.

B. Probability of not activating while establishing a quorum of ratio τ

In the recent quorum sensing literature, some articles have identified and studied a phenomenon known as *cheating* [20].

TABLE I
MAXIMIZERS AND MAXIMA OF THE PAY-OFF FUNCTIONS IN FIG. 3.

τ	$\alpha^\star$	$\mathcal{J}^\star$
0.90	44	42.6989
0.75	61	30.9052
0.50	101	13.4081
0.25	191	2.0214

TABLE II
MAXIMIZERS AND MAXIMA OF THE PAY-OFF FUNCTIONS IN FIG. 4.

c	$\alpha^\star$	$\mathcal{J}^\star$
25	27	50.5373
50	61	30.9052
75	96	17.3499
100	138	9.0366

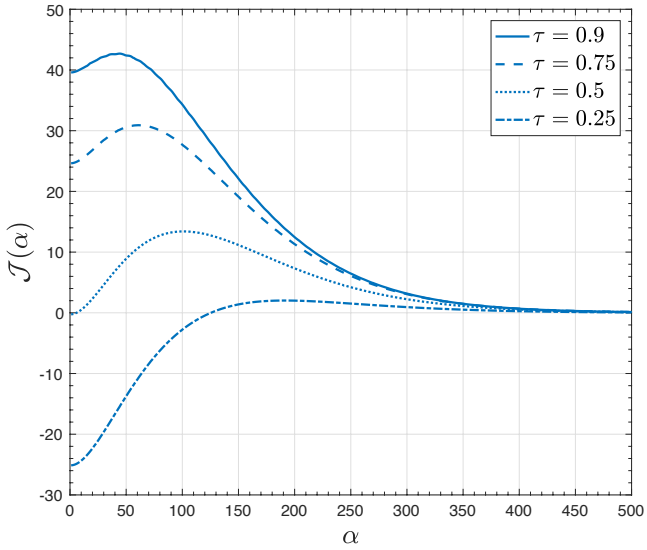

Fig. 3. Pay-off function of the local activation threshold α for several values of the quorum ratio τ.

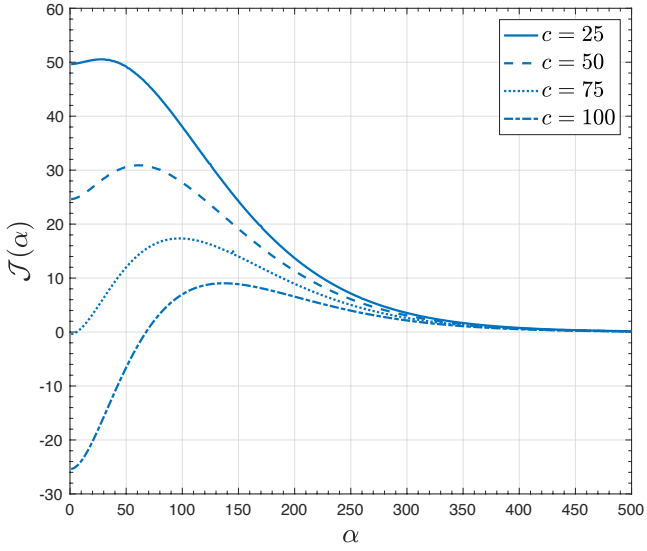

Fig. 4. Pay-off function of the local activation threshold α for several values of the local activation cost c.

In the economics literature, a similar phenomenon is known as *free-riding*. A cheater or free-rider is defined as a cell that decides not to 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 cheating. Furthermore, this phenomenon can be observed and quantified in experimental setups where the activation is visualized by fluorescence.

The probability of the i-th cell not activating given that quorum of ratio τ was formed is defined as

$$\mathbf{P}_{free}(\tau) \stackrel{\text{def}}{=} \mathbf{P}\big(A_i = 0 \mid L(X) \geq \tau \lfloor X \rfloor\big). \tag{17}$$

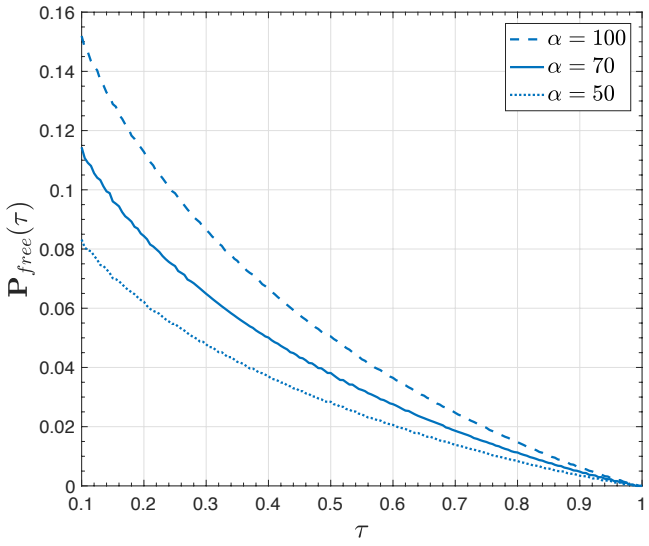

Fig. 5. Probability of not activating given that a quorum of ratio τ was formed for several values of the local activation threshold α.

This probability can be computed in terms of quantities previously defined in Eqs. (13) and (15).

Proposition 2: Consider the quorum sensing system of Problem 1. The probability of the i-th cell not activating given that a quorum of ratio τ is formed, can be computed as follows

$$\mathbf{P}_{free}(\tau) = \frac{\mathbf{E}\Big[\mathbf{P}(\sum_{j\neq i} A_j \geq \tau\lfloor X\rfloor \mid X)\cdot \mathbf{P}(A_i = 0 \mid X)\Big]}{\mathbf{E}\Big[\mathbf{P}(L(X) \geq \tau\lfloor X\rfloor \mid X)\Big]}, \tag{18}$$

where the expectations are with respect to X,

$$\mathbf{P}(A_i = 0 \mid X = x) = 1 - p(x;\alpha,\lambda), \tag{19}$$

and that given $X = x$,

$$\sum_{j\neq i} A_j \sim \text{Binomial}\big(\lfloor x\rfloor - 1, p(x;\alpha,\lambda)\big). \tag{20}$$

Proof: The proof follows from iterated expectations, Bayes' rule and conditional mutual independence of A_i, $i \in \{1,\cdots,\lfloor X\rfloor\}$ given X. ∎

The probability of free-riding as a function of τ is shown in Fig. 5 for a prior distribution with parameters $\kappa = 2$ and $\theta = 50$. We observe that $\mathbf{P}_{free}$ is a decreasing function of τ and is increasing in α. The probability of free-riding is connected to the activation cost c in the following way: for larger values of c, the optimal value of the activation threshold $\alpha^\star$ is also larger, yielding a higher probability of cheating. In a dynamic problem setting where the concentration of cells and auto-inducers change with time, this probability allows us to predict the fraction of the population that will activate within a time-interval. Another benefit of being able to compute the probability of cheating is that it is useful for estimating the parameter τ from experimental data, as we will do in the next section.

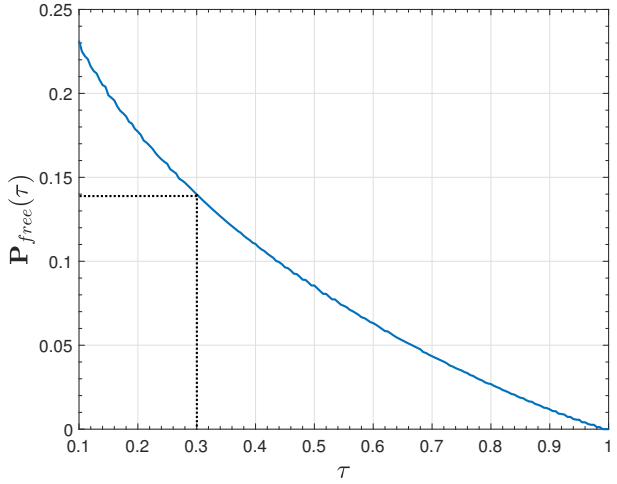

Fig. 6. Probability of not activating given that a quorum of ratio τ is formed for a prior distribution of parameters $\kappa = 5.5780$ and $\theta = 5.6770$, and activation threshold $\alpha = 70$.

IV. Model Calibration

In this section we discuss preliminary experimental results on the validation of our mathematical model using the bacteria strain *E. coli ptd103 LuxI/R*, which produces an fluorescence exofactor. It has been documented, e.g. [18], that this strain uses thresholds $\alpha = 70$nM and its production rate of auto-inducer molecules per cell is

$$\lambda = 2.3 \times 10^{-9}\text{nmol}. \tag{21}$$

In our experiments, the total volume occupied by the colony was fixed to 5ml and the activity in colony can be observed as in Fig. 8. Typically, the data collected in quorum sensing experiments is a time series. Our one-shot optimization problem formulation 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 $\alpha = 70$, we predict that the state transition occurs at approximately $t = 5$h. Fitting a Gamma density to our collected data, we obtain the parameters $\kappa = 5.5780$ and $\theta = 5.6770$ Billion cells/L. Since $\lambda X \sim \mathcal{G}(\kappa, \lambda\theta)$, we have

$$\lambda X \sim \mathcal{G}(5.5780, 13.0572). \tag{22}$$

From our experimental data, we counted the fraction of cells that have activated at time $t = 5$h. Its complement gives us an estimate of the probability of not activating given that quorum was established, from which the quorum ratio τ can be estimated, i.e.,

$$\mathbf{P}_{free}(\tau) \approx 0.14 \Longrightarrow \hat{\boldsymbol{\tau}} \approx \mathbf{0.3}, \tag{23}$$

where the value of $\hat{\tau}$ was obtained from Fig. 6. Finally, the last part in our model calibration is to estimate the value of c. This is done by knowing that for this strain of bacteria the optimal activation threshold is $\alpha^\star = 70$. Looking for the value of c that gives us this value of $\alpha^\star$, we obtain $\hat{\boldsymbol{c}} \approx \mathbf{20.25}$.

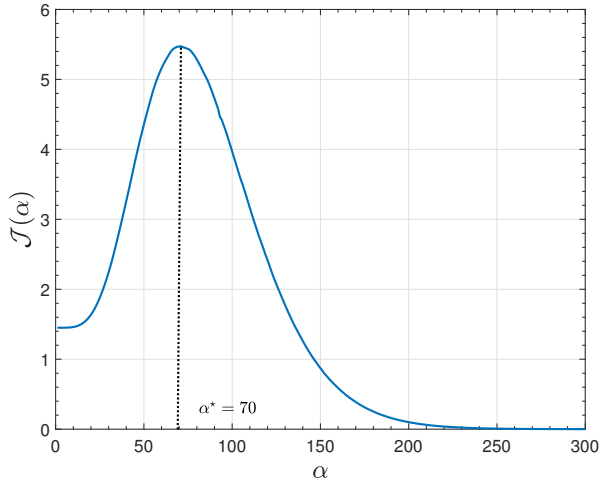

Fig. 7. Pay-off function that the bacterial colony studied in our experiments is optimizing. According to our model, the local activation cost is equal to $c = 20.25$.

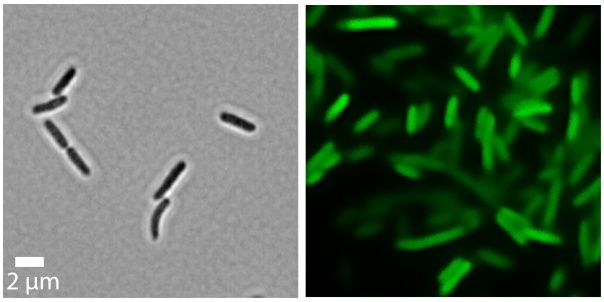

Fig. 8. Our experimental data was collected from microscopic images such as the ones above, where the total number of cells and the total number of activated (fluorescent) cells is estimated.

V. Conclusion and Future Work

This paper proposes a new optimization based framework for studying quorum sensing as a networked decision system. Our framework admits a simple description that at the same time allows for mathematical analysis, captures many features known to exist in quorum sensing systems and can be extended to accommodate the interaction between multiple colonies. Future work on this model will include: noncooperative game theoretic formulations, where each bacteria uses different thresholds and seek a Nash-equilibrium solution; and sequential problem formulations, where the signaling population dynamics and signaling play a major role on how information is disseminated over the colony. We plan to use the insights gained from this future analysis to mathematically show how bacteria have developed quorum sensing mechanisms that aggregate information in an optimal way.

TABLE III
Experimental Data

t (h)	$\bar{X}$ (10^9 cells/L)	σ_X (10^9 cells/L)	$\lambda\bar{X}$ (nM)	p
0	0.0465	0.0140	0.1070	0
1	0.0653	0.0011	0.1503	0
2	0.4267	0.0833	0.9813	0
3	0.6400	0.1637	1.4720	0.0135
4	4.0667	0.5033	9.3533	0.1038
5	**31.6667**	**13.4079**	**72.8333**	**0.8538**
6	147.3333	93.0017	338.8667	0.9953
7	262.6667	68.8573	604.1333	1

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