A sequential decision making model of bacterial growth via quorum sensing

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***Abstract*—Quorum sensing is a mechanism used by bacteria to coordinate the expression of certain exofactors which are more beneficial at higher cell densities. It has been argued that quorum sensing is a way for bacteria to control gene expression where some performance metric is being optimized. Herein, bacterial growth via quorum sensing is studied under the lens of optimal control theory. Under the assumption of perfect state observation, it is shown that quorum sensing is an optimal control strategy for an infinite horizon discounted reward function.**

I. Introduction

Bacteria are simple unicellular organisms able to perform complex collective tasks very effectively at high population. This is achieved by means of a mechanism known as *quorum sensing* (QS), where each bacterial cell secretes small molecules in the environment called *auto-inducers*. Each bacterium is able to measure the concentration of auto-inducers in the environment, which allows it to estimate the population of the bacterial colony. Once the population exceeds a certain threshold, the cells start producing *exofactors* responsible for certain tasks such as: degrading antibiotics, metabolizing food, luminescence and biofilm formation.

Consider, for example, the case when QS is used to regulate the production of enzymes responsible for metabolizing food. The production of this exofactor is costly to the cell but, once released in the environment, it benefits the entire colony. In this context, when the concentration of enzymes (public-good) is high enough, more food will be available for every cell in the colony and therefore, the colony will be able to achieve a larger population (public benefit). This scenario is akin to problems of (human) population growth in the Economics literature, e.g. [1]. However, the mathematical model for bacterial population growth is unique [2], and classical results from the existing literature in this area are not applicable to our problem.

Our goal is to formulate and solve a discrete-time sequential optimization problem where each cell in the colony decides at each time step whether to engage or not in the production of a costly exofactor that leads to the long term increase in the maximum achievable population. Under the assumption of perfect observation of the state of the system, the problem introduced herein admits an analytical solution through optimal control theory. We show that the optimal growth curve is attained by employing a threshold policy on the population, where the optimal thresholding variable is computed in closed form as a function of parameters of the system.

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A. Literature review and summary of contributions

Quorum sensing was discovered in 1970 in the context of growth of luminous bacteria *Aliivibrio fischeri* [3]. Since then, quorum sensing has been found to be a general strategy for coordinating group behavior in many species of bacteria [4]. A survey of the of the history of QS and a summary of the main results in this research area can be found in [5] and references therein.

There exist many mathematical models for QS. The classic approach used in the literature consists in describing the evolution of the concentration of chemical signal, enzymes and bacteria in the environment, using coupled deterministic differential equations. An alternative stochastic model that uses Queuing Theory has been proposed to analyze QS systems in [6]. A growing portion of the recent QS literature assumes that each bacterium can be considered as a decision-making unit with the goal of optimizing the performance of the colony [7]. Within this new paradigm, the optimization of certain parameters of the QS system have been studied under different performance metrics.

The optimization of the "sensing potential" was studied in [8], where the overall fitness of the cells in a colony is defined as the benefit gained minus the cost incurred from producing exofactors. A similar approach was used in [9] where QS was modeled as a networked decision system, where each cell is an agent whose actions have local costs but global impact on "fitness" of the colony. The fitness of the colony is proportional to the growth rate of its population. Early frameworks to study such optimization problems were introduced in [10] and [11] where dynamics is considered, but optimality was solely measured in terms of the instantaneous population at a given time. We argue that in order to properly perform optimization in a sequential decision making model of QS, it is necessary to define a reward function that takes into account not only the present, but also future populations. The proper mathematical tool to analyze such problems is optimal control theory, e.g. [12].

The key contributions of this work are to:

- Provide a QS model that incorporate dynamics and sequential optimization of population growth that resembles classic problems from Economics, but are tailored to bacterial colonies.
- Solve the problem analytically, under the assumption of perfect observation on the current population, obtaining a structural result on the optimal control policy as a threshold policy.
- Compute the optimal threshold in closed form as a function of the parameters of the system.

II. The Model

We start with the discrete-time *Logistic Population Growth* (LPG) model [13]. Let $x[n]$ denote the concentration of population at time n, such that $x[n] \in \mathbb{R}_{\geq 0}$ for all $n \in \{0, 1, \cdots\}$. We assume that samples are taken every hour. One can think of n as the number of hours passed since an experiment has started. According to LPG dynamics, the concentration of population of the colony evolves as follows:

$$x[n+1] = \left[x[n] + \lambda \cdot x[n] \left(1 - \frac{x[n]}{\kappa} \right) \right]^+, \tag{1}$$

where $[a]^+ \stackrel{\text{def}}{=} \max\{a, 0\}$, $a \in \mathbb{R}$. The dynamical system in Eq. (1) is characterized by two parameters λ and κ, which correspond to the *intrinsic growth-rate* and the *carrying capacity*, respectively.

Quorum sensing is typically described by a pair of controlled difference equations that describe the dynamics of the signal $s[n]$ and the enzymes $e[n]$, where the control signal $u[n]$ is a number between 0 and 1 that represents the fraction of active cells in the colony. The following equation describes the evolution of the concentration of auto-inducer molecules:

$$s[n] = (1 - \gamma_s)s[n-1] + x[n]\big(1 + \sigma_s u[n]\big). \tag{2}$$

Notice that at every sample time n, the population injects $x[n]$ units of auto-inducer molecules in the environment (here we will only consider normalized quantities). Auto-inducer molecules degrade at a rate γ_s units per time step. One interesting feature of QS mechanisms is that once activated, the cells produce auto-inducers at a higher rate. This is captured by the constant σ_s, also referred to as the positive feedback rate. The second difference equation used to describe a QS mechanism is:

$$e[n] = (1 - \gamma_e)e[n-1] + x[n]\sigma_e u[n]. \tag{3}$$

In that equation, γ_e is the degradation rate of the enzymes produced by the cells. It is assumed that enzymes are produced at a rate σ_e units per time step only when the cells are active.

The control signal $u[n]$ is computed according to a policy $\mathcal{U}$, which is a function of the observable signal $s[n]$,

$$u[n] = \mathcal{U}\big(s[n]\big). \tag{4}$$

However, under the assumption of homogeneous cells making noiseless measurements of the concentration of auto-inducer molecules $s[n]$, the colony is either entirely active or inactive, that is,

$$u[n] \in \{0, 1\}. \tag{5}$$

In our model, we will assume that a *social planner* controls the activation policy such as to optimize the performance of the system. The goal of the social planner is to maximize a discounted objective function of the form:

$$\mathcal{V}(x_0) \stackrel{\text{def}}{=} \sum_{n=0}^{\infty} \beta^n \big(1 - \alpha u[n]\big) x[n], \tag{6}$$

where $\beta \in (0, 1)$ is the intertemporal discount factor, $\alpha \geq 0$ captures the energetic activation cost, and x_0 is the initial population.

A. Public-goods and local activation cost

We adopt a production of public-goods interpretation to QS, e.g. [11]. The public-goods are the enzymes that are being released in the environment and are used, for instance, to metabolize food. The enzymes act as public-goods because once they are released in the environment, their byproduct will be enjoyed by the entire colony. The production of enzymes is costly and is reflected in the growth rate of our LPG model, i.e., when the colony is active, it grows at a slower rate (λ decreases). Therefore, let the controlled intrinsic growth rate be defined as follows:

$$\lambda[n] \stackrel{\text{def}}{=} \rho - c u[n], \tag{7}$$

where $\rho \in [0, 1]$ is the (normalized) autonomous growth rate and c is a real number between 0 and ρ. The reason why this is a realistic assumption is that the cells must spend a considerable amount of energy to produce the enzymes and thus less energy is available for cell division.

B. Public benefit

The consequence of having a higher concentration of public-goods is that there will be more food available in the environment. In that case, the overall condition of the colony will be improved by increasing the carrying capacity of the system. Herein, the public benefit is the net gain in carrying capacity. The carrying capacity is the maximum number of cells that the environment is able to support for an extended period of time. Typically, the public benefit function in these types of problems are characterized by a few properties [11]:

1) The benefit is an increasing function of the concentration of public-good.
2) The benefit does not increase indefinitely as the concentration of public-good increases; it saturates at some finite value.
3) The benefit is zero when there is no public-good present.

One family that satisfies these properties is the class *soft-thresholding* functions [11]. The class is characterized by three parameters, $b_{\max}$, τ and h and is defined as:

$$\Delta\kappa_h(e) \stackrel{\text{def}}{=} b_{\max} \cdot \frac{(e/\tau)^h}{1 + (e/\tau)^h}, \tag{8}$$

where $b_{\max} \geq 0$, $\tau \geq 0$ and $h > 1$. The parameter τ is defined as the quantity of public-goods that yields half of the maximum benefit, $b_{\max}$. The parameter h controls the steepness of the transition from zero to maximum benefit.

III. A sequential optimization problem

The optimization problem posed in the previous section is one of optimal control with partial observations of the system state, $x[n]$. This is because the cells in a real QS system can only measure $s[n]$ and not $x[n]$ directly. In order to obtain a tractable sequential optimization problem and corresponding analytical results, we make the following assumptions:

1) The system has no memory, i.e., the signal and enzyme degradation rate constants are equal to one:

$$\gamma_s = \gamma_e = 1. \tag{9}$$

This means that, at each time step, the signal produced by the cells is completely degraded before the next sample time.

2) There is no positive feedback in the signal equation, i.e.,

$$\sigma_s = 0. \tag{10}$$

These two assumptions lead to the following pair of equations for the signal and enzyme concentrations:

$$s[n] = x[n] \tag{11}$$
$$e[n] = x[n]\sigma_e u[n]. \tag{12}$$

This means that the state of the system is now directly observed by the cells, admitting a direct analysis without the use of an intermediate observer to estimate the system state prior to computing the control signal.

Finally, for tractability, we will assume $h = \infty$, so that the public benefit in Eq. (8) becomes:

$$\Delta\kappa_\infty(e) = b_{\max} \cdot \mathbf{1}(e \geq \tau), \tag{13}$$

which implies that the carrying capacity of the system is given by:

$$\kappa[n] = \kappa_0 + (\kappa_1 - \kappa_0)\mathbf{1}(e[n] \geq \tau), \tag{14}$$

where $\mathbf{1}(\cdot)$ denotes the indicator function[1], and $\kappa_1 > \kappa_0$. The interpretation is that once the concentration of enzymes in the environment exceeds the threshold τ, the carrying capacity of the system increases from κ_0 to κ_1.

Using Eq. (12), the controlled carrying capacity of the system is given by:

$$\kappa[n] = \kappa_0 + (\kappa_1 - \kappa_0) \cdot \mathbf{1}(x[n]\sigma_e u[n] \geq \tau). \tag{15}$$

Therefore, if $u[n] = 0$ (the colony is "off"):

$$\kappa[n] = \kappa_0. \tag{16}$$

And if $u[n] = 1$ (the colony is "on"):

$$\kappa[n] = \kappa_0 + (\kappa_1 - \kappa_0)\mathbf{1}(x[n] \geq \tau/\sigma_e). \tag{17}$$

Lastly, plug in Eqs. (7) and (17) into Eq. (1) to define:

$$\mathcal{F}(x,u) \stackrel{\text{def}}{=} \left[x + (\rho - cu)x\left(1 - \frac{x}{\kappa_0 + (\kappa_1 - \kappa_0)\mathbf{1}(xu \geq m)}\right)\right]^+, \tag{18}$$

where $m \stackrel{\text{def}}{=} \tau/\sigma_e$, resulting in the dynamical system:

$$x[n+1] = \mathcal{F}\big(x[n], u[n]\big). \tag{19}$$

IV. Analysis

In order to solve the optimal control problem, we must find the solution to the following functional Bellman equation [12]:

$$\mathcal{V}(x) = \max_{u \in \{0,1\}} \Big\{(1 - \alpha u)x + \beta \mathcal{V}\big(\mathcal{F}(x,u)\big)\Big\}. \tag{20}$$

In this section, we present a closed form solution for the optimal policy obtained from the solution of the Bellman equation above when $\alpha = 0$.

[1]The indicator function is defined as:

$$\mathbf{1}(\mathfrak{S}) \stackrel{\text{def}}{=} \begin{cases} 1 & \text{if } \mathfrak{S} \text{ is true} \\ 0 & \text{otherwise.} \end{cases}$$

Theorem 1: Let $m < \kappa_0$. If $\alpha = 0$, the optimal solution for the optimization problem under the assumptions in Eqs. (9), (10) and (14) is a threshold policy of the form:

$$\mathcal{U}^*(x) = \mathbf{1}(x \geq x^*), \tag{21}$$

where

$$x^* = \begin{cases} m & \text{if } \ c \leq \frac{\rho(\kappa_1 - \kappa_0)m}{\kappa_0(\kappa_1 - m)} \\ \frac{c\kappa_0\kappa_1}{(\kappa_1 - \kappa_0)\rho + c\kappa_0} & \text{otherwise.} \end{cases} \tag{22}$$

Before proving Theorem 1 we need the following lemma.

Lemma 1: Let $m < \kappa_0$. The value function $\mathcal{V}$ obtained as the unique solution of Eq. (20) is strictly increasing.

Proof: We use a well known fact that the solution to the Bellman equation can be found through a procedure called *value function iteration* [12]. Start with a initial function $\mathcal{V}^{(0)}(x)$ and generate a sequence of functions according to the following recursion:

$$\mathcal{V}^{(n+1)}(x) = x + \beta \max_{u \in \{0,1\}} \Big\{\mathcal{V}^{(n)}\big(\mathcal{F}(x,u)\big)\Big\}. \tag{23}$$

This sequence converges to a unique value function $\mathcal{V}$ regardless of $\mathcal{V}^{(0)}$. Our proof consists of initializing the sequence with a strictly increasing function and showing that every function $\mathcal{V}^{(n)}$ generated through value function iteration is also strictly increasing.

The proof is by induction on n. Let $\mathcal{V}^{(0)}(x) = x$, which is strictly increasing. Assume that $\mathcal{V}^{(n)}$ is strictly increasing. Then, if follows that:

$$\mathcal{V}^{(n+1)}(x) = x + \beta\mathcal{V}^{(n)}\Big(\max\big\{\mathcal{F}(x,0), \mathcal{F}(x,1)\big\}\Big). \tag{24}$$

It can be shown that $\mathcal{F}(x,0)$ is strictly increasing on the interval $[0, k_0]$, and $\mathcal{F}(x,1)$ is strictly increasing on the interval $[0, k_1]$. Moreover,

$$\mathcal{F}(x,1) > \mathcal{F}(x,0), \quad x \in [\kappa_0, \kappa_1]. \tag{25}$$

Therefore, $\max\big\{\mathcal{F}(x,0), \mathcal{F}(x,1)\big\}$ is strictly increasing on $[0, \kappa_1]$, which implies that $\mathcal{V}^{(n+1)}(x)$ is also strictly increasing on $[0, \kappa_1]$.

We argue that the limit of the sequence defined by Eq. (23), $\mathcal{V}$, is a strictly increasing function. Suppose that $\mathcal{V}$ were simply increasing, then another iteration of Eq. (23) would produce a strictly increasing function due to the addition of the strictly increasing function x. ∎

Proof of Theorem 1: If $\alpha = 0$, Eq. (20) can be written as:

$$\mathcal{V}(x) = x + \beta \max\Bigg\{\mathcal{V}\left(x + \rho x\Big(1 - \frac{x}{\kappa_0}\Big)\right), \mathcal{V}\left(x + (\rho - c)x\Big(1 - \frac{x}{\kappa_0 + (\kappa_1 - \kappa_0)\mathbf{1}(x \geq m)}\Big)\right)\Bigg\}. \tag{26}$$

From Lemma 1, the value function $\mathcal{V}$ is a strictly increasing function, which implies that:

$$\mathcal{V}\left(x + \rho x\Big(1 - \frac{x}{\kappa_0}\Big)\right) = \mathcal{V}\left(x + \Big(\rho - c)x(1 - \frac{x}{\kappa_0 + (\kappa_1 - \kappa_0)\mathbf{1}(x \geq m)}\Big)\right) \tag{27}$$

if and only if

$$x+\rho x\Big(1-\frac{x}{\kappa_0}\Big)= x+(\rho-c)x\Big(1-\frac{x}{\kappa_0+(\kappa_1-\kappa_0)\mathbf{1}(x\geq m)}\Big). \quad (28)$$

After some algebra and rearranging the terms in Eq. (28), we get:

$$cx=\left(\frac{\rho}{\kappa_0}-\frac{\rho-c}{\kappa_0+(\kappa_1-\kappa_0)\mathbf{1}(x\geq m)}\right)x^2 \quad (29)$$

Let $\mathcal{G}$ be defined as

$$\mathcal{G}(x)\stackrel{\text{def}}{=}\left(\frac{\rho}{\kappa_0}-\frac{\rho-c}{\kappa_0+(\kappa_1-\kappa_0)\mathbf{1}(x\geq m)}\right)x^2. \quad (30)$$

If $x<m$, then

$$\mathcal{G}(x)=\left(\frac{c}{\kappa_0}\right)x^2. \quad (31)$$

Since $m<\kappa_0$, we have:

$$\mathcal{G}(m)=cm\left(\frac{m}{\kappa_0}\right)<cm. \quad (32)$$

If $x\geq m$, then

$$\mathcal{G}(x)=\left(\frac{(\kappa_1-\kappa_0)\rho+c\kappa_0}{\kappa_0\kappa_1}\right)x^2. \quad (33)$$

It is straightforward to show that if

$$c\geq\frac{\rho(\kappa_1-\kappa_0)m}{\kappa_0(\kappa_1-m)} \quad (34)$$

then

$$\mathcal{G}(m)\geq cm. \quad (35)$$

Therefore,

$$x^*=m. \quad (36)$$

On the other hand, if

$$c<\frac{\rho(\kappa_1-\kappa_0)m}{\kappa_0(\kappa_1-m)} \quad (37)$$

then, the optimal threshold x^* is the unique nonzero solution of the following equation:

$$cx^*=\left(\frac{(\kappa_1-\kappa_0)\rho+c\kappa_0}{\kappa_0\kappa_1}\right)(x^*)^2. \quad (38)$$

i.e.,

$$\left(c-\frac{(\kappa_1-\kappa_0)\rho+c\kappa_0}{\kappa_0\kappa_1}x^*\right)x^*=0. \quad (39)$$

Therefore,

$$x^*=\frac{c\kappa_0\kappa_1}{(\kappa_1-\kappa_0)\rho+c\kappa_0}. \quad (40)$$

■

The optimal solution for the case when $\alpha=0$ stated in Theorem 1 does not depend on the discount factor β. This is because the cost and benefit are experienced instantaneously by the cells in the colony. Therefore, there is no intertemporal trade-off in this instance of the problem. As we will show in Section V, the dependence on β appears when $\alpha>0$. However, in that case, Eq. (20) must be solved numerically.

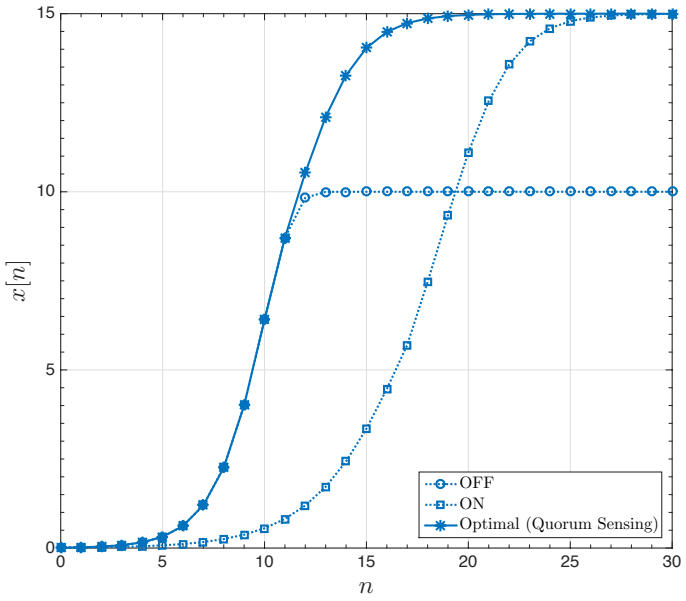

Fig. 1. Growth curves obtained for our model in Example 1. In that case, $\alpha=0$ and the optimal threshold can be computed using the closed form expression given by Theorem 1.

There are other scenarios where such intertemporal trade-offs play a major role. Consider another version of our model, where the decrease in intrinsic growth rate is experienced instantaneously, but the higher capacity is experienced with a unit delay, i.e.,

$$\lambda[n]=\rho-cu[n] \quad (41)$$

and

$$\kappa[n+1]=\kappa_0+(\kappa_1-\kappa_0)\mathbf{1}(e[n]\geq\tau). \quad (42)$$

The delay in Eq. (42) is accounted for the time it takes for the enzymes to break down the food that will be consumed in the future by the colony. This interesting case is currently under investigation.

Notice that due to the structure of the problem, we were able to solve the optimal control problem without explicitly finding the value function $\mathcal{V}$.

Example 1: In order to illustrate the result in Theorem 1, we considered the following instance of our model with $\alpha=0$, $\kappa_0=10$, $\kappa_1=15$, $m=5$, $\rho=1$, $c=0.5$ and $x[0]=0.01$. Computing the optimal threshold in the statement of Theorem 1, gives:

$$x^*=7.5.$$

The optimal growth equation is given by the following expression:

$$x[n+1]=x[n]+(\rho-c\mathbf{1}\big(x[n]\geq x^*\big)\times x[n]\left(1-\frac{x[n]}{\kappa_0+(\kappa_1-\kappa_0)\mathbf{1}(x[n]\geq x^*)}\right), \quad (43)$$

Figure 1 shows the optimal growth curve alongside the ones obtained using the "on" $\big(\mathcal{U}(x)\equiv 0\big)$ and "off" $\big(\mathcal{U}(x)\equiv 1\big)$ policies. The corresponding values of each policy are listed in Table I.

TABLE I
VALUE OF THE OBJECTIVE FUNCTION $\mathcal{V}(0.01)$ FOR $\alpha = 0$.

β	$\mathcal{V}_{\text{off}}$	$\mathcal{V}_{\text{on}}$	$\mathcal{V}_{\text{qs}}$
0.7	1.4384	0.3076	1.5626
0.8	6.4535	2.0898	7.5829
0.9	37.0031	24.3931	48.4066

TABLE II
VALUE OF THE OBJECTIVE FUNCTION $\mathcal{V}(0.01)$ FOR $\alpha = 0.1$.

β	$\mathcal{V}_{\text{off}}$	$\mathcal{V}_{\text{on}}$	x^*	$\mathcal{V}_{\text{qs}}$
0.7	1.4384	0.2769	8.6485	1.4871
0.8	6.4535	1.8809	8.3642	7.0527
0.9	37.0031	21.9538	8.1522	44.1733

V. THE GENERAL CASE

When $\alpha > 0$, i.e., there is an explicit cost for activation in the objective function, and a dependency on the discount factor appears in the optimal threshold. However, the solution of Eq. (20) needs to be computed numerically.

Consider Eq. (20) with $\alpha > 0$:

$$\mathcal{V}(x) = x + \beta \max\left\{\mathcal{V}\big(\mathcal{F}(x,0)\big), \mathcal{V}\big(\mathcal{F}(x,1)\big) - \frac{\alpha}{\beta}x\right\}. \quad (44)$$

After computing the value function $\mathcal{V}$ as the unique solution to Eq. (44), we can compute the optimal threshold by solving the following equation:

$$\mathcal{V}\big(\mathcal{F}(x^*,0)\big) = \mathcal{V}\big(\mathcal{F}(x^*,1)\big) - \frac{\alpha}{\beta}x^*. \quad (45)$$

Example 2: Consider the following instance of our model with $\alpha = 0.1$, $\kappa_0 = 10$, $\kappa_1 = 15$, $m = 5$, $\rho = 1$, $c = 0.5$. Using the numerical procedure outlined above, we can compute the optimal threshold x^* as a function of the discount factor β, which is displayed in Fig. 2. Notice that the optimal activation threshold when $\beta \leq 0.44$ is equal to $\kappa_0 = 10$. This means that for values of the discount factor below 0.44, the colony will not activate since κ_0 is the carrying capacity of the unactivated system. Table II lists the value of the "on", "off" and optimal policy for different values of β.

VI. CONCLUSIONS

We approach quorum sensing from the point of view of optimal control theory. Our model consists of colony of bacteria whose population grows according to a modified logistic dynamics, where the rate of growth and the carrying capacity are controlled. The goal is to optimize a discounted objective function of the population of cells in the colony. We show that, when the state of the system is perfectly observed, the optimal control strategy has a threshold structure on the population. We computed the optimal threshold in closed form as a function of the parameters of the system. Future work will address systems with partial observations; consider objective functions with different structures; and validate our results using experimental data.

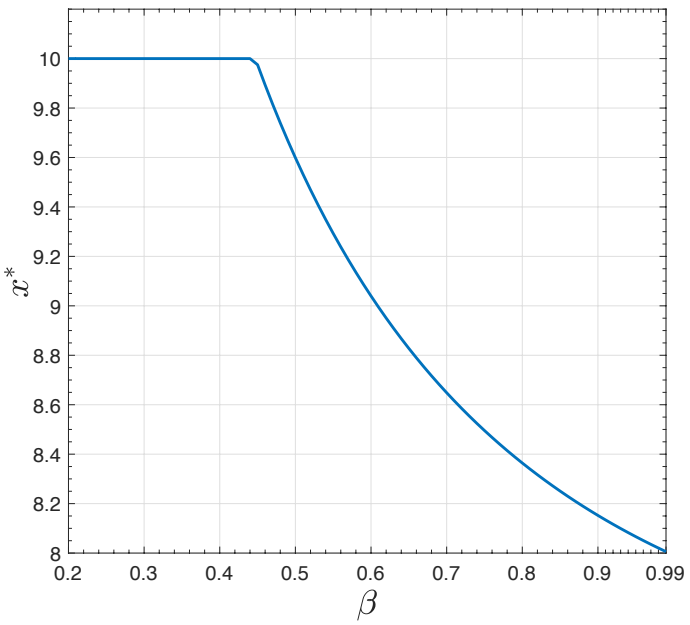

Fig. 2. Optimal threshold as a function of the discount factor β and the parameters of the system from Example 2.

REFERENCES

[1] A. Razin and U. Ben-Zion, "An intergenerational model of population growth," *The American Economic Review*, vol. 65, no. 5, pp. 923–933, December 1975.

[2] D. M. Cornforth, D. J. T. Sumpter, S. P. Brown, and Å. Brännström, "Synergy and group size in microbial cooperation," *The American Naturalist*, vol. 180, no. 3, pp. 296–305, September 2012.

[3] K. Nealson, T. Platt, and J. Hastings, "The cellular control of the synthesis and activity of the bacterial luminescent system," *Journal of Bacteriology*, vol. 1, no. 104, pp. 313–322, 1970.

[4] C. M. Waters and B. L. Bassler, "Quorum sensing: Cell-to-cell communication in bacteria," *Annual Review of Cell and Developmental Biology*, vol. 21, pp. 319–346, November 2005.

[5] J. Boedicker and K. Nealson, "Microbial communication via quorum sensing," *IEEE Transactions on Molecular, Biological, and Multi-scale Communications*, vol. 1, no. 4, pp. 310–320, December 2015.

[6] N. Michelusi, J. Boedicker, M. Y. El-Naggar, and U. Mitra, "Queuing models for abstracting interactions in bacterial communities," *IEEE Journal on Selected Areas in Communications*, vol. 34, no. 3, pp. 584–599, March 2016.

[7] L. Castelli, R. Pesenti, and D. Segrè, "The cell as a decision-making unit," *IEEE Life Sciences Letters*, vol. 2, no. 3, pp. 27–30, September 2016.

[8] A. Pai and L. You, "Optimal tuning of bacterial sensing potential," *Molecular Systems Biology*, vol. 5, no. 1, p. 286, January 2009.

[9] M. M. Vasconcelos, U. Mitra, O. Camara, K. P. Silva, and J. Boedicker, "Bacterial quorum sensing as a networked decision system," in *IEEE International Conference on Communications*, 2018, pp. 1938–1883.

[10] A. Pai, Y. Tanouchi, and L. You, "Optimality and robustness in quorum sensing (QS)-mediated regulation of a costly public good enzyme," *Proceedings of the National Academy of Sciences*, vol. 109, no. 48, pp. 19 810–19 815, 2012.

[11] S. Heilmann, S. Krishna, and B. Kerr, "Why do bacteria regulate public goods by quorum sensing? – how the shapes of cost and benefit functions determine the form of optimal regulation," *Frontiers in Microbiology*, vol. 6, no. 767, pp. 1–11, July 2015.

[12] L. Ljungqvist and T. J. Sargent, *Recursive Macroeconomic Theory*. The MIT Press, 2000.

[13] R. M. May, "Simple mathematical models with very complicated dynamics," *Nature*, no. 261, pp. 459–467, June 1976.