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EMERGENCE OF COLONY-LEVEL QUORUM SENSING DUE TO EXPANSION BASED ON SIMPLE DYNAMICS

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Abstract. The growth of bacterial colonies is described in terms of a simple mathematical model that incorporates aspects of nutrient acquisition and quorum sensing signal molecule production. Quorum sensing describes cell communication mechanism that allows bacterial cells to control colony's behaviour in relation to the population density. The consecutive relation of cell transition and quorum sensing signal molecule production is explored using a continuum representation. This paper demonstrates a simple interaction model for non-motile bacteria based on existing mathematical descriptions. The model considers the population of bacteria as consisting of down-regulated and up-regulated bacteria in which the signal molecules being produced at much faster rate by the up-regulated bacteria. The finding highlights the existence of fold bifurcation phenomenon on the fraction of up-regulated bacteria that behaves as an "on-off" quorum sensing switch in response to the effective diffusion constant.

Keywords: simple mathematical model; bacterial colony; quorum sensing; diffusion; fold bifurcation.

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1. INTRODUCTION

In the environment, unicellular bacteria are typically found in communal groups, colonies or biofilms [1, 2]. In a similar manner to multicellular organisms, bacteria have the ability to build and manage complex social interactions to exhibit diverse behavioural responses [3, 4, 5].

The bacterial interactions are associated with biological and physical processes, such as growth, transitions (differentiation and consolidation), wetting agent production processes [6], and quorum sensing signal molecule production [7]. This paper investigates colony growth with a mathematical model that is affected by nutrient concentration and signal molecule production. Bacteria assess population density via quorum sensing (QS; [8]). The process of quorum sensing is regulated by the production and monitoring of chemical signal molecule that increase in concentration as a function of cell density [9, 10]. Cells produce, detect, and release low-molecular-mass signal molecules called autoinducers, or recently quormon [1, 11]. However, Gory et al. [12] suggest that most of the signal molecules are lost to the environment by diffusion.

Kleerebezem et al. [13] explained the different signalling mechanisms of Gram-positive and Gram-negative bacteria. Particularly, Gram-negative bacteria sense their population density using *accylated homoserine lactones* (AHLs), and Gram-positive bacteria use oligo-peptides that diffuse through the cell membrane. In Gram-negative bacteria, quorum sensing is normally controlled by a small gene expression network that functions as a switch [14, 15, 16]. QS allow bacteria to switch over from off-QS to on-QS related with low and high cell density behaviours [1, 17, 18]. Moreover, Henke and Bassler [19] state that bacteria will respond as a community to change target gene expression switch if they achieved a certain threshold concentration of autoinducer. When the condition of cell density is low, that usually corresponds to the "off" switch state, the bacterial cells continuously produce a small amount of QS signal molecules that can diffuse in and out of the cells. As the cell density increases, so does the concentration of autoinducers. After a certain population density of cells is passed, quorum is achieved and the autoinducer signal causes the switch of the QS network to the "on" state. Besides that, once the bacterial colony has reached the particular threshold of QS signal molecules, so the corresponding bacterial behaviour will be switched "on" [10]. This paper employs data on the colony

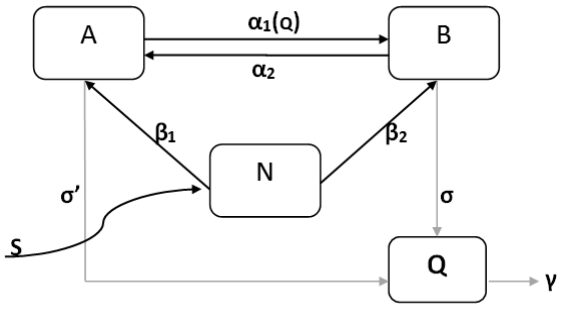


FIGURE 1. A simple model to illustrate the bacterial interaction involved growth and transition processes. Solid line represent transfer biomass and transparent line represent that bacteria produce QS signal molecules

growth and QS signal molecules production of Gram-negative plant pathogen, *Erwinia carotovora* as an example. Then, construct a simple mathematical model of bacterial interaction. The purpose is to establish a rational description that can be used to explain the colony-level quorum switch as the colony expands.

In section 2, this paper describes in greater detail the biological system as well as the mathematical approach. In section 3, this paper analyses fixed points and bifurcation phenomenon that occur in the system. Throughout the paper makes reference to the experimental data of Byers et al. [20], and set parameter values using data for *E. carotovora* in section 4. Finally, in section 5 this paper discusses the results, and improvements to the theory.

2. MATHEMATICAL MODEL

The following non-spatial model gives specialized attention to nutrient acquisition and QS signal molecule production on non-motile bacterial colonies and involves four dependent variables: N for the concentration of nutrients, A for biomass of down-regulated bacteria with quorum sensing circuits switched off (off-QS), B for biomass of up-regulated bacteria with quorum sensing circuits switched on (on-QS), and Q for the concentration of signal molecules. Nutrient acquisition influences the growth and activities of the bacterial colony. The model is summarized in the schematic in Fig. 1.

The biomass of non-motile bacteria with off-QS (A) is formed via the law of mass action at growth rate β_1. It is increased and decreased through the transition process of non-motile

bacteria with on-QS (B) to off-QS (A) and vice versa, at rate α_2 and α_1, respectively. Thus the biomass of bacteria (A) can be modelled as

$$\frac{dA}{dt} = \frac{\beta_1 NA}{K+N} + \alpha_2 B - \alpha_1(Q)A. \tag{1}$$

In a similar manner, this paper formulates an equation for the biomass of non-motile bacteria with on-QS (B) at bacterial growth rate β_2 are modelled such that

$$\frac{dB}{dt} = \frac{\beta_2 NB}{K+N} + \alpha_1(Q)A - \alpha_2 B. \tag{2}$$

For simplicity down-regulated and up-regulated are assumed to have the same growth rate, $\beta_1 = \beta_2$.

It is clear that nutrient in the suspension is consumed by both off-QS and on-QS bacteria. The rate of change of nutrient, N, can be written as

$$\frac{dN}{dt} = S - \frac{\beta_1 NA}{K+N} - \frac{\beta_2 NB}{K+N} \tag{3}$$

where S is a nutrient source term.

2.1. Ratios of bacterial biomass.

To make analytical progress, this paper defines new variables

$$x = \frac{A}{A+B} \qquad \text{and} \qquad y = \frac{B}{A+B}. \tag{4}$$

Here, x is the ratio between the amount of biomass of off-QS bacteria and the total biomass, and y is the ratio between the amount of biomass of on-QS bacteria and the total biomass. Hence, $x+y=1$, and substituting into equations (1) and (2) yields

$$\begin{aligned} \frac{dx}{dt} &= \left(\frac{\beta_1 N}{K+N}\right)xy + \alpha_2 y^2 - \alpha_1 xy - \left(\frac{\beta_2 N}{K+N}\right)xy - \alpha_1 x^2 + \alpha_2 xy, \\ \frac{dy}{dt} &= \left(\frac{\beta_2 N}{K+N}\right)xy + \alpha_1 x^2 - \alpha_2 xy - \left(\frac{\beta_1 N}{K+N}\right)xy - \alpha_2 y^2 + \alpha_1 xy. \end{aligned} \tag{5}$$

From above differential equation system (5), this paper has solution that x in proportion to the rate of change transition A over total rate of change transition A and B, such that $\left(\frac{\alpha_1}{\alpha_1+\alpha_2}\right)$. The amount of x decrease to certain value, then reach remain stable condition in that value. Conversely, the amount of y increase up to particular level and remain at that level.

In the mathematical model (Fig. 1), the model assumes both bacteria A and B produce QS signal molecule with constant rates σ' and σ with $\sigma' << \sigma$. The signal molecules produced may be lost from the system due to diffusion. Thus the concentration of QS signal molecules changes as

$$\frac{dQ}{dt} = \sigma' A + \sigma B - \gamma Q, \tag{6}$$

where γ represents the rate of loss of signal molecules via both degradation and diffusion from the system.

As with x and y, a more tractable variable is the amount of signal molecules per bacterium, q, defined as

$$q = \frac{Q}{A+B}. \tag{7}$$

The amount of signal molecules influences the transition rate α_1 between off-QS and on-QS bacteria. Thus α_1 represents a function of the amount of signal molecules, which can be written in the base mathematical model $\alpha_1(Q)$. Associated with the amount of biomass and the concentration of signal molecules per bacterium, α_1 is described as transition rate, such that $\alpha_1(q)$. Following Langebrake et al. [21], the transition rate from off-QS to on-QS bacteria can be approximately modelled with a Hill function of the form $\alpha_1(q) = C_0 + (C_1 - C_0)\frac{q^n}{\kappa^n + q^n}$, providing control over the location of the transition [22]. Thus there are three phases in the transition process. This is consistent with evidence from molecular biology for both *Vibrio fischeri* and the related QS system, suggesting that the signal molecule binds as a ligand to the DNA, which promotes the operon that produces more QS molecules [23].

The four parameters of the Hill equation are C_0, C_1, κ and n. The Hill function coefficient n determines the shape; the value of the Hill coefficient $n > 1$ describes positively cooperative binding. For this case, the model also consider the tangent hyperbolic function as a suitable replacement for the Hill function in order to obtain analytic solutions for the bifurcation points. It can describe the transition process properly, and is defined by $\alpha_1 = C_0 + (C_1 - C_0)\tanh(\kappa(q - q_0))$, where κ is a constant that determines the slope transition rate from off-QS to on-QS bacteria, replacing the Hill function coefficient (n). This function also allows control over the location of transition. Thus the amount of signal molecules to switch

between the phases varies with the particular parameter of the transition rate, α_1. Meanwhile, the model assumes that the transition rate from on-QS to off-QS, α_2, is a constant.

2.2. Ratios of bacterial biomass.

Let τ be the total amount of biomass of bacteria, such that

$$\tau = A + B. \tag{8}$$

For the sake of simplicity, here this paper shall assume the shape of the culture is a cylindrical slab. Thus the total amount of biomass of bacteria (τ) is proportional to the volume of culture $\left(\pi r^2 h\right)$. The model also assumes the increase of bacterial cells leads to the proportional growth of colony radius and nutrient is accessible to the colony. All new growth of bacterial cells is immediately transferred to the colony edge, while the death of bacterial cells results in decrease in the cell density locally. Consequently, the model can justify that the entire area of the culture is occupied by nutrient source (S). In relation to these assumptions, the nutrient source (S) is not only proportional to the radius of culture (r), but also to the square root of total amount of biomass $(\tau^{1/2})$. Therefore, if the radius of bacterial colony is assumed to increase linearly with time, the increase rate of total biomass is

$$\frac{d\tau}{dt} = C\tau^{1/2}, \tag{9}$$

where C is a constant, and the production rate of signal molecules per bacterium is

$$\frac{dq}{dt} = \sigma'(1-y) + \sigma y - q\left(\gamma + \delta\tau^{-\frac{1}{2}}\right). \tag{10}$$

If it is assumed that $\gamma' := \gamma + \delta\tau^{-\frac{1}{2}}$ changes at a slower rate than the other processes, then it obtains γ' as a control parameter. Hence,

$$\frac{dq}{dt} = \sigma'(1-y) + \sigma y - q\gamma' \quad \text{or} \quad \sigma' x + \sigma(1-x) - q\gamma'. \tag{11}$$

Here γ' represents an effective rate of loss of the QS molecules, which decreases slowly over a long time scale as the colony grows. By applying the assumption that the bacterial colonies to have the same growth rate for both types ($\beta_1 = \beta_2$), this paper can construct the relation between

signal molecules and biomass of bacteria, which can be described by the pair of equations,

$$\begin{aligned} \frac{dy}{dt} &= \alpha_1(1-y) - \alpha_2 y, \\ \frac{dq}{dt} &= \sigma'(1-y) + \sigma y - q\gamma'. \end{aligned} \tag{12}$$

It is reasonable to assume that the production of QS molecule is much faster than cell growth, thus $\frac{dq}{dt}$ tends to 0 relative quickly. If the value of γ' is considered as a constant, it obtains that the amount of signal molecule q in proportion to y, such that,

$$q = \frac{\sigma'(1-y) + \sigma y}{\gamma'}. \tag{13}$$

As $\sigma' \ll \sigma$, $q \approx \frac{\sigma y}{\gamma'}$ may substitute into $\frac{dy}{dt}$, so that it becomes

$$\frac{dy}{dt} = \left(C_0 + (C_1 - C_0)\tanh\left(\kappa\left(\frac{\sigma y}{\gamma'} - q_0\right)\right)\right)(1-y) - \alpha_2 y, \tag{14}$$

where κ represents the slope of the transition rate.

3. Analysis of Fixed Points and Bifurcation

Fixed points (steady states) are points at which time derivatives vanish [24]. For the current system, steady states correspond to a constant fraction of up-regulated bacteria within the system, even though the amount of up-regulated bacteria may continue to increase or decrease.

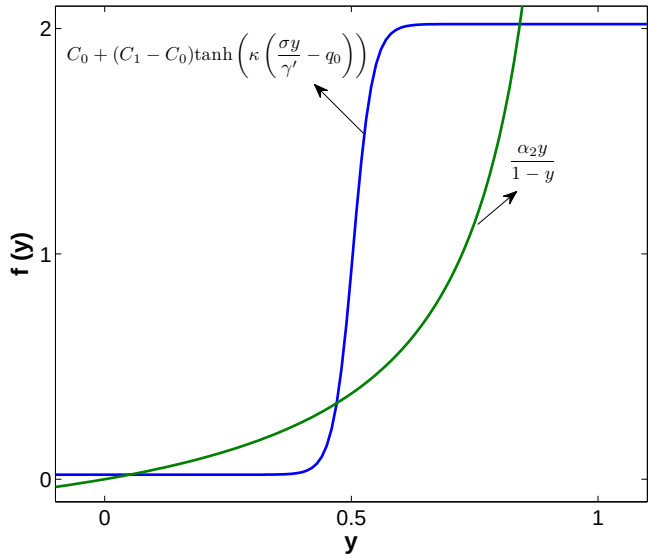
The steady states are given by the solution of $\frac{dy}{dt} = 0$. To assist graphical analysis the equation for the steady state of (14) can be written as

$$C_0 + (C_1 - C_0)\tanh\left(\kappa\left(\frac{\sigma y}{\gamma'} - q_0\right)\right) = \frac{\alpha_2 y}{1-y}. \tag{15}$$

The right-hand term is a curve with asymptote at $y = 1$, and the left-hand term represents a hyperbolic function.

The curves have three intersection points that can be seen in Fig. 2. As explained before, transition processes between off-QS and on-QS bacteria are typically modelled with Hill functions. If the model had used a Hill function instead the model would need $n \geq 3$ in order to get bifurcation phenomenon related with an "on-off" switch. Instead, the model use the tangent hyperbolic function to allow for a relatively simple analytic solution.

(a)



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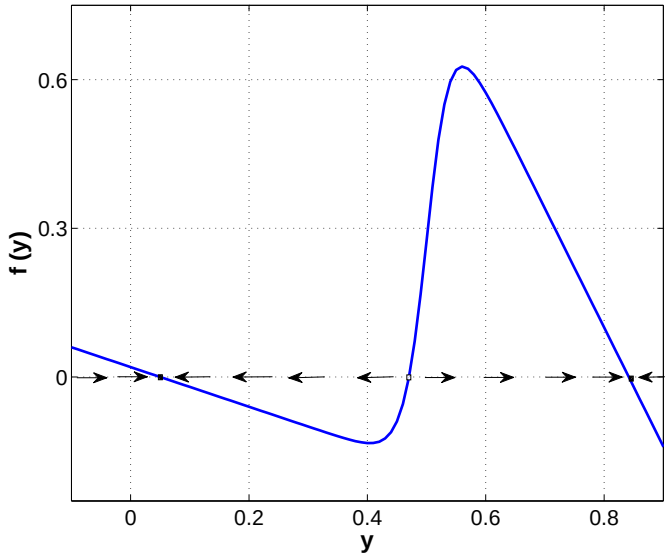


FIGURE 2. Three solutions are found in figure (a) as the intersections of curve $\alpha_2 y/(1-y)$ and curve $C_0 + (C_1 - C_0)\tanh(\kappa(\sigma y/\gamma' - q_0))$. The slope of the curve at the intersection determines the stability of fixed points. (b) The stability of fixed points of $f(y)$. Here, $C_0 = 1.02$, $C_1 = 2.02$, $\sigma = 7.72 \times 10^{-6}$, $\alpha_2 = 0.38$, $\gamma' = 4.86 \times 10^{-5}$, and $\kappa = 40$.

Varying the values of parameters in the model modifies the qualitative structure of the flow and controls the fold bifurcation appearance [25]. A saddle-node bifurcation occurs when the gradients of the two sides of (15) match, such that

$$\kappa\frac{\sigma}{\gamma'}\left(1-\tanh^2\left(\kappa\left(y\frac{\sigma}{\gamma'}-q_0\right)\right)\right)=\frac{1}{C_1-C_0}\frac{\alpha_2}{(1-y)^2}. \tag{16}$$

Substituting (15) into (16) yields

$$\frac{\kappa\sigma}{\alpha_2\gamma'}\left((C_1-C_0)(1-y)^2-\frac{\alpha_2^2y^2}{C_1-C_0}+\frac{2\alpha_2C_0y(1-y)}{C_1-C_0}-\frac{C_0^2(1-y)^2}{C_1-C_0}\right)=1. \tag{17}$$

It is clear that $\frac{\kappa\sigma}{\alpha_2\gamma'}\neq 0$, thus

$$\alpha_2=\frac{(2C_0y-C_0)\pm\sqrt{(C_0-2C_0y)^2+(y-y^2)\left(8C_1C_0-4C_1^2\right)}}{-2y}. \tag{18}$$

Furthermore, (14) can be written in the form

$$\kappa=\frac{\gamma'}{\sigma y-\gamma' q_0}\operatorname{arctanh}\left(\frac{\alpha_2y-C_0+C_0y}{(C_1-C_0)(1-y)}\right). \tag{19}$$

Substituting (18) into (19) gives

$$\kappa=\frac{\gamma'}{\sigma y-\gamma' q_0}\times \operatorname{arctanh}\left(\frac{-C_0\pm\sqrt{(C_0-2C_0y)^2+y\left(8C_1C_0-4C_1^2\right)-y\left(8C_1C_0-4C_1^2\right)^2}}{2(C_1-C_0)(1-y)}\right). \tag{20}$$

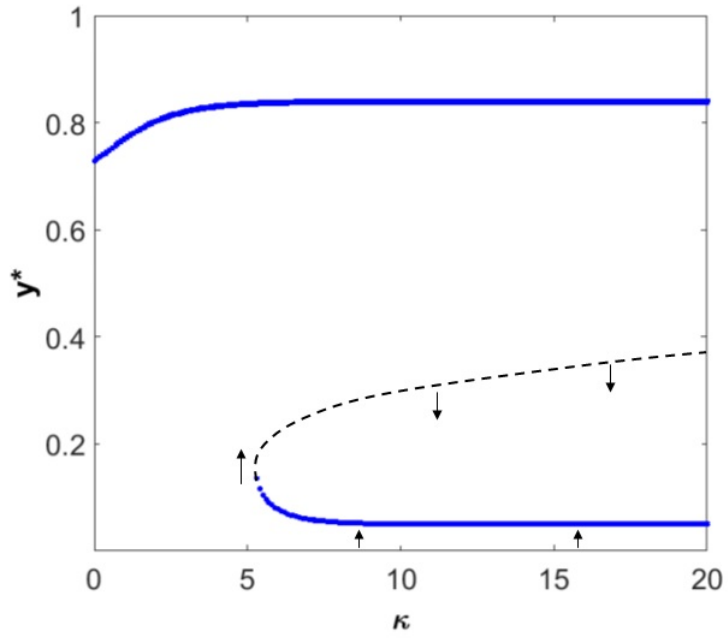
By using the same way the calculation of bifurcation, this paper can get bifurcation diagram with γ' as bifurcation parameter. Substituting $\alpha_2(y)$ into (15) yields

$$\gamma'=\frac{\sigma\kappa y}{\left(\kappa q_0+\operatorname{arctanh}\left(\frac{-C_0\pm\sqrt{(C_0-2C_0y)^2+y\left(8C_1C_0-4C_1^2\right)-y\left(8C_1C_0-4C_1^2\right)^2}}{2(C_1-C_0)(1-y)}\right)\right)}. \tag{21}$$

The multiple steady states due to variation of parameter values affect bifurcation occurrence [26]. This can be easily seen by analyzing the steady state in the system for some values of parameter. Two stable steady states coexist and are separated by an unstable region [27].

The parameter κ affects the stability of the system as it determines the shifted slope of the transition rate from off-QS to on-QS bacteria. If κ has small positive values, there is only one point of intersection. However, above a certain positive value of κ, there are three intersection

(a)



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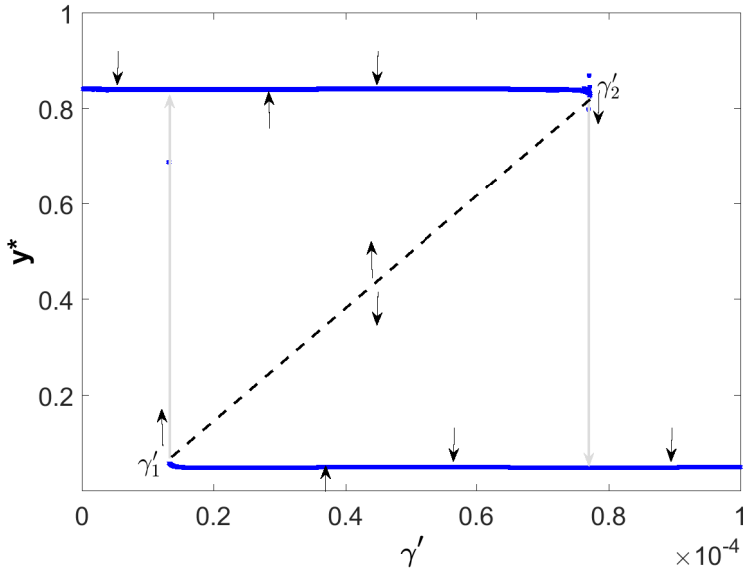


FIGURE 3. Bifurcation diagrams. The arrows indicate the direction of change from the unstable states to stable states. The stable states are represented by solid lines on the upper and lower branches, while unstable states are represented by a dashed line in the middle section. (a) κ as bifurcation parameter and $\gamma' = 4.86 \times 10^{-5}$. (b) γ' as bifurcation parameter and $\kappa = 40$. Other parameter values are $C_0 = 1.02$, $C_1 = 2.02$, $\sigma = 7.72 \times 10^{-6}$, and $\alpha_2 = 0.38$.

points: associated with two stable and one unstable steady state. The bifurcation diagram (Fig. 3a) shows that with κ as bifurcation parameter the system has only one bifurcation point a fold bifurcation. For certain high positive values of κ, the gradient of the transition curve will only change slightly as this paper employs a hyperbolic function $(tanh)$ that determines the slope of transition. There is almost no change in the steady states for large values of κ. As a consequence, there is no collision of the high and intermediate steady states. They will never meet for the large κ.

Fig. 3b explains that if γ' is very large, then the stable points of the fractional up-regulated bacteria are very low, corresponding to the "off" state. As γ' is decreased, it moves through the bistable region until γ' reaches γ'_1 and y^* shifts discontinuously to the higher state. Such shifting induces a higher production of QS signal molecules that corresponds to the "on" state. Conversely, when γ' increases to γ'_2, y^* shifts discontinuously to the lower state, which results in a lower production of QS signal molecules that corresponds to the "off" state.

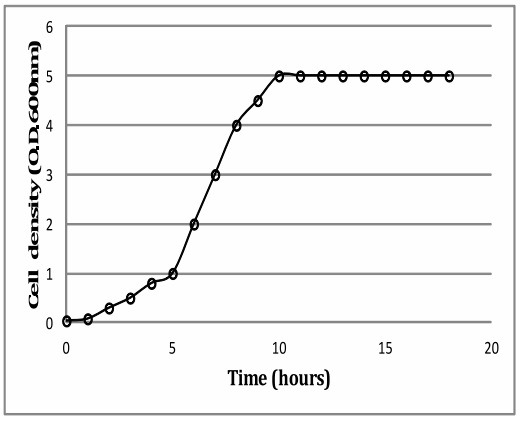
4. Estimation of Parameter

The model parameters represent rates of the bacterial interactions involving cell growth, signal molecule production and diffusion, and cell transition. Values for several parameters, including β_1, β_2, σ and γ', were taken from experimental data, related to previous work [20]. Other parameter values, α_1 and α_2 can be inferred from the model to investigate bifurcation phenomena.

The value of bacterial growth rate (based on assumption that β_1 and β_2 have similar values) is obtained from the rate of change cell density in exponential phase. The value of γ is calculated based on the decay phase of signal molecules concentration, where the model assumes that there is no signal molecule production during the decay phase. From the mathematical model in the previous section, this paper have assumed that the rate-of-change of bacteria cells is determined by growth rate (β_1) and amount of bacteria (B), such that $B = B_0 e^{\beta_1 t}$ where B_0 represents initial amount of bacteria. Thus, the differential equation for signal molecules Q becomes

$$\frac{dQ}{dt} = \sigma B_0 e^{\beta_1 t} - \gamma Q, \tag{22}$$

(a)



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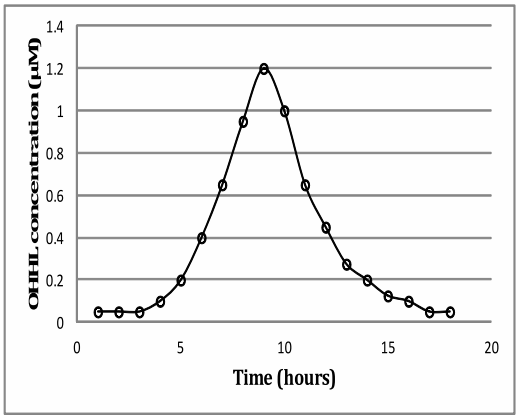

FIGURE 4. (a) bacterial growth and (b) signal molecule (OHHL) concentration, as obtained from experiment on *E. carotovora*. Replotted from data in Byers et al. 2001, pp 1165.

and there is an equation for Q that can be used to obtain the value of the signal molecule production rate (σ), which is

$$Q = \frac{\sigma}{\beta_1 + \gamma} B_0 e^{\beta_1 t} + C e^{-\gamma t}. \tag{23}$$

Table 1 lists some parameter values from above calculation taken from Byers et al. [20], either obtained from the graph $(\beta_1, \beta_2,$ and $\gamma)$ or the equation (σ), whereas the parameter value of α_2 (transition rate "off "to "on") remains difficult to determine a specific number. The reason for

TABLE 1. Parameter estimates for simple model of non-motile bacterial interactions.

Name	Value	Unit	Description	Ref
β_1	2.78×10^{-4}	s^{-1}	growth rate of bacteria off-QS	[20]
β_2	2.78×10^{-4}	s^{-1}	growth rate of bacteria on-QS	[20]
σ	7.72×10^{-6}	$\mu m s^{-1}$	signal molecules production rate	[20]
γ	4.86×10^{-5}	$\mu m s^{-1}$	signal molecules diffusion rate	[20]
α_2	0.38	s^{-1}	transition rate on-QS to off-QS	estimated

this corresponds to the fact that determining the exact value is quite complicated. Many papers have focused on explaining temporal transition between "off " to "on " state, and conversely [e.g. Ward et al. [10] states that a corresponding bacterial colony will "switch on" their trait depending on their density once a specific concentration of Q is reached. Goryachev et al. [28] and Langebrake et al. [21] investigate interim transitions between "off and on " state]. In this case, the parameter value for the transition rate is an arbitrary constant chosen to obtain bistability behaviour. This is a familiar behaviour that represents the dynamical system of the QS signal molecule. The bacteria have a low steady state (off) from which it is possible to jump past an unstable state to a stable high steady state (on) [29, 10].

The results in Fig. 4, provide the value of bacterial growth rate, $\beta_1 = 2.78 \times 10^{-4}\ /s$ (β_2 as well). They also give the value of loss rate of signal molecules is $\gamma = 4.86 \times 10^{-5}\ \mu m/s$. Then, from the equation of Q, it obtains $\sigma = 7.72 \times 10^{-6} \mu m/s$.

5. RESULTS AND DISCUSSION

This paper have presented a simple model of bacterial interaction that gives particular attention to nutrient acquisition and QS signal molecule production as an important aspect of the transition rate of bacterial types. This develops the model through specifying the dynamics of off-QS and on-QS non-motile bacteria.

In the simulations, several different parameter values are tested and the outputs consistently showed the same behaviour. The parameter values used were adopted from Byers et al. [20]; This paper employs data on *E. carotovora* to proceed the model. From the simulation this paper

shows the relation between cell transition rate and the amount of QS signal molecule. The increase of QS signal molecule concentration raises the transition rate (from off-QS to on-QS of bacteria). In order to explore the dynamical behaviour of the proposed model, a bifurcation analysis has been carried out by considering the slope transition rate from off-QS to on-QS bacteria (κ) and loss effective rate of signal molecules (γ') as bifurcation parameters. The system has a fixed point solution which exhibits a fold bifurcation. The numerical result shows that an effective rate of diffusion of the QS signal molecule decreases on a slow time scale as the colony grows. In a related study, Ward et al. [10] found switching behaviour for *Vibrio fischeri* in which there was a cell transition as the colony increased in size. Ward et al. [10] presented a mathematical model which describes bacterial population growth and quorum sensing. The population of bacteria consist of down-regulated and up-regulated sub-populations, with signal molecules being produced at a much faster rate by the up-regulated cells.

The hysteresis phenomenon is predicted by the model, yet it has not been verified experimentally. In addition, the model sets the bacterial colonies to have the same growth rate for both types. In contrast, bacterial colonies have different growth rate that depends on temperature and light [30], availability of nutrient [28]. In that regard, it would be more interesting to use assumptions that can resemble real conditions by considering factors that influence the growth rate of bacteria through experiment.

Bees et al. [31] state that there will be translocation and expansion through surfaces of medium by swarming bacterial colonies to get access to a wider source of nutrient, which is a main factor in establishing the success of a specified colony. In addition, sufficient nutrient acquisition promotes formation of the flagellar that enables bacteria to be more active and expand to the larger area. This expectation is in accordance with Kim et al. [32], who show the supply of higher nutrient concentration produces more active cells.

Furthermore considering the theoretical research regarding QS systems, the results need to be developed into regulation system of QS model in order to look deeply of bistability phenomena on QS signal molecule behaviour per se. James et al. [23] demonstrated QS model of *V. fischeri*, which has two stable metabolic states corresponding to the expression of the luminescent and non-luminescent phenotypes. The system has three steady states that has a “switch-like”

behaviour. In simultaneous work, Dockery and Keener [29] showed the biochemical switch between two stable steady states on QS model of *P. aeruginosa*, one with low level and another one with high level of signal molecules, is the key to how QS works in relation to the population density. Like James et al. [23], Dockery and Keener [29] developed a model of a QS system of *P. aeruginosa* and presented that the system has two steady states which are regulated by signal molecules. Therefore, these works will motivate researchers to look in more detail at the biochemical behaviour of QS systems.

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CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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