# Chapter 12
# Anti-quorum Sensing Systems and Biofilm Formation


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## Contents



**Abstract** Bacterial communication process can be broadly classified into two categories such as chemical communication process (quorum sensing mechanism) and electrical communication system (controlled by potassium ion channels). Quorum sensing is a well-known density-dependent optimal survival strategy, which is mediated by chemical signalling molecules (autoinducers). Collective bacterial behaviour regulates the bacterial lifestyle on surface (i.e. biofilms). Bacterial cell-to-cell communication process and biofilms formation cause several infectious diseases. In this chapter, we mainly focus on anti-quorum sensing mechanism and biofilm formation (including nanofabrication) that form the point of view of experimental approaches as well as mathematical models. In the end, we point out some significant and fundamental experimental observations on anti-quorum sensing and biofilm formation.

**Keywords** Bacteria · Biofilms · Anti-quorum sensing · Nanofabrication

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## 12.1 Introduction

Bacteria can communicate with their surrounding bacteria by using chemical signalling communication systems. This chemical signalling mechanism is formally known as quorum sensing (Fuqua et al. 1996; Gray et al. 1994). Microbiologists intensively studied this critical biochemical phenomenon to understand the information processing system of different bacteria and their collective behaviour in the last few decades. Bacterial communication system is controlled by autoinducers (chemical signalling molecules). Bacteria prepare their optimal survival strategies to survive in a different environment by using different quorum sensing circuits (Miller and Bassler 2001; Williams et al. 2007; Shapiro 1998). Quorum sensing bacteria eject autoinducers in the environment and the surrounding bacteria receive autoinducers. In this fashion, the concentration of the autoinducers increases as a function of cell number density (Shapiro 2007; Majumdar and Mondal 2016; Majumdar and Pal 2016, 2017a, b; Majumdar et al. 2017). When the concentration reaches as minimal threshold, a collective bacterial behaviour is initiated, which triggers cascade of signalling events and regulate an array of biochemical process such as biofilm formation, swarming, virulence, bioluminescence, symbiosis, competence, antibiotic production, sporulation, conjugation and gene expression (Majumdar and Pal 2018; Majumdar and Roy 2018a, b).

Bacterial biofilms are considered as a collective bacterial living form, where bacterial cells are embedded in an extracellular polymeric substance (EPS) that are adherent to each other and a surface (Vert et al. 2012). Bacterial biofilms have different emergent properties such as localized gradient, sorption, enzyme retention, tolerance and resistance, competition and cooperation (Flemming et al. 2016). The mechanical stability of the biofilm is provided by EPS. EPS are lipids, nucleic acid, proteins and polysaccharides (Flemming and Wingender 2010). Pathogenic bacteria are harmful for human. This bacteria community living culture (i.e. biofilms) is a cause of different infectious diseases such as urinary tract, synthetic vascular grafts, gastrointestinal tract, dental implant, cardiac implant and many more (Majumdar and Roy 2018a, b).

## 12.2 Anti-quorum Sensing Model

We are discussing anti-quorum sensing models, which describe anti-quorum sensing treatment in biofilms and batch cultures. This model is based on LasI/R system of *P. aeruginosa* and applicable for LuxI/R homolog systems. The bacterial population can be assumed as two subpopulations such as up-regulated cells and down-regulated cells (Ward 2008; Anguige et al. 2004, 2005, 2006).

- $N_d$ represents the down-regulated cell density. The cells contain empty *lux*-box. *P. aeruginosa* produce autoinducers and EPS matrix at a low rate. A nonvirulent activity is observed at that situation.

- $N_u$ represents the up-regulated cell density. Cells have complex (LasR-autoinducer) bound *lux*-box. The autoinducers and EPS are produced at enhanced rate. Virulent activity is observed.
- Total bacterial population density is $N_T = N_d + N_u$.
- Down-regulated cell divides into two down-regulated cells.
- Up-regulated cell divides into one down-regulated and one up-regulated cell.
- We assume that LasR (with concentration $R$) is generated at rate $R_0$ and binds with autoinducer $A$ (reversable reaction) and form complex $P$ (LasR-autoinducer). We get,
- $\frac{dR}{dt} = R_0 - k_{\text{ra}}AR + k_pP - \lambda_R R$ and LasR-autoinducer complex equation $\frac{dP}{dt} = k_{\text{ra}}AR - k_pP - \lambda_pP$. Output of LasI (up-regulated cells) occurs at constantrate and decays as follows $\frac{dL}{dt} = L_0 - \lambda_L L$ (see Fig. 12.1).
- Autoinducers are generated with a background level $k_d$ and decay with constant $\lambda$. The rate of change of autoinducer (down-regulated cells) $= k_d - k_{\text{ra}}AR + k_pP - \lambda A$.
- The rate of change of autoinducers (up-regulated cells) $= k_aL + k_d - k_{\text{ra}}AR + k_pP - \lambda A$, where $k_aL$ shows a massive increase (up-regulated cells) of autoinducers production. $-\lambda A$ describes the rate of change of autoinducers (external media).
- If $\frac{dR}{dt} = \frac{dP}{dt} = \frac{dL}{dt} = 0$ (equilibrium condition) then $L = L_\infty$,

$$P = \frac{P_\infty}{R_\infty}RA, \quad R = \frac{R_\infty}{1+\mu_R A}, \quad \text{where} \quad L_\infty = \frac{L_0}{\lambda_L}, \quad R_\infty = \frac{R_0}{\lambda_R}, \quad \mu_R = \lambda_pP_\infty \Big/ \lambda_R R_\infty$$

and $P_\infty = R_\infty k_{\text{ra}} \Big/ \left(k_p + \lambda_p\right)$.

- With the substitution $R = R_\infty$, $\mu_R A \approx 0$ and $P = P_\infty A$, we have the rate of change of autoinducers (down-regulated cells) $= k_d - \sigma A - \lambda A$ and the rate of change of autoinducers (up-regulated cells) $= k_u + k_d - \sigma A - \lambda A$, where $\sigma = \lambda_p P_\infty$ and $k_u = k_a L_\infty$.
- We assume that up-regulation rate of bacterial cells is proportional to $P_\infty A$ (complex concentration). So, up-regulation rate is $\alpha A$, where $\alpha = \alpha_a P_\infty$ and $\alpha_a$ is proportionality constant. The down-regulation rate of cells is $\beta = \lambda_p$.
- Let $Q_1$, $Q_2$, $Q_3$ be the concentration of the anti-LuxR (homolog) agent, anti-autoinducer agent and anti-LuxI (homolog) agent respectively which follows.

$$\text{LasR} + Q_1 \xrightarrow{k_1} \left(1 - v_1\right)Q_1 + \text{by product}$$

$$\text{Autoinducer} + Q_2 \xrightarrow{\mu_2} \left(1 - v_2\right)Q_2 + \text{by product}$$

$$\text{Autoinducer} + Q_3 \xrightarrow{\mu_3} (1 - v_3)Q_3 + \text{by product}$$

- where $v_1$, $v_2$, $v_3$ represent the average amount of $Q_1$, $Q_2$, $Q_3$ lost by the reaction respectively.
- So, we find LasR concentration (at equilibrium) is $R = R_\infty / (1 + \gamma_1 Q_1)$, where $\gamma_1 = \frac{k_1}{k_R}$. Moreover, LasR-autoinducer binding rate and up-regulation rate is reduced by the factor $(1 + \gamma_1 Q_1)$.
- We find $-\mu_2 Q_2 A$ as an additional term in equation of rate of change of autoinducers (up-regulated and down-regulated cells).
- LasI equilibrium level reduces to $L_\infty/(1 + \gamma_3 Q_3)$, where $\gamma_3 = k_3 / \lambda_L$. The new autoinducer output rate term is $k_u/(1 + \gamma_3 Q_3)$.

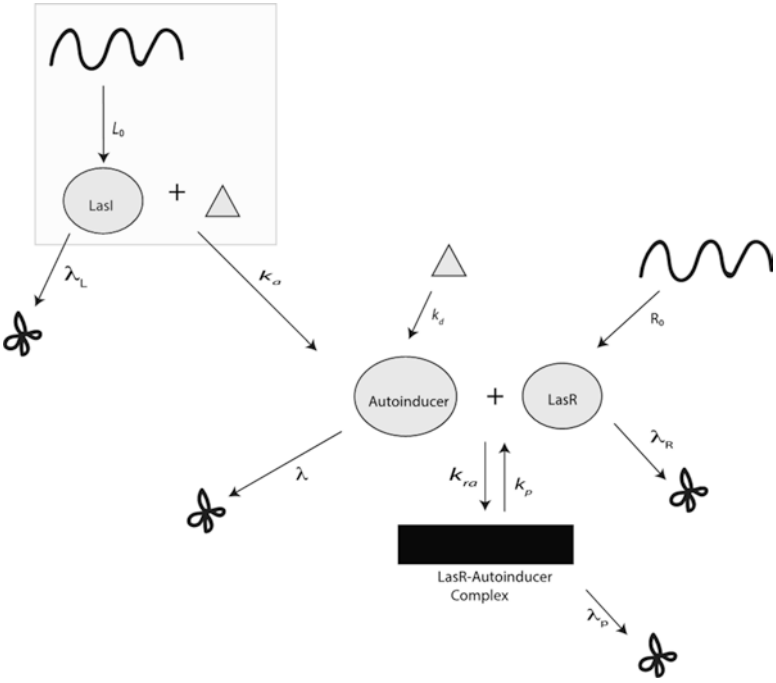


**Fig. 12.1** Schematic visualization of *P. aeruginosa* quorum sensing process (LasI/LasR system), which is used for the mathematical modelling approach. The rectangular box represents a reaction for up-regulated cells only and wavy line represents the transcription of protein

### 12.2.1 Mathematical Model of Anti-quorum Sensing Treatment (in Batch Culture)

Now, we assume that the parameters of mathematical model are continuous in space and time. In this modelling approach, we neglect the stochastic effects. The following set of equations are based on the above assumptions (Ward 2008; Anguige et al. 2004, 2005, 2006):

$$\frac{dN_d}{dt} = rN_T - \frac{\alpha A}{1+\gamma_1 Q_1} N_d + \beta N_u \tag{12.1}$$

$$\frac{dN_u}{dt} = \frac{\alpha A}{1+\gamma_1 Q_1} N_d - \beta N_u \tag{12.2}$$

$$\frac{dA}{dt} = \frac{k_u}{1+\gamma_3 Q_3} N_u + k_d N_T - \frac{\sigma A}{1+\gamma_1 Q_1} N_T - \lambda A - \mu_2 Q_2 A \tag{12.3}$$

$$\frac{dQ_1}{dt} = \phi_1 - \frac{\mu_1 Q_1}{1+\gamma_1 Q_1} N_T - \lambda_1 Q_1 \tag{12.4}$$

$$\frac{dQ_2}{dt} = \phi_2 - \mu_2 v_2 A Q_2 - \lambda_2 Q_2 \tag{12.5}$$

$$\frac{dQ_3}{dt} = \phi_3 - \frac{\mu_3 Q_3}{1+\gamma_3 Q_3} N_u - \lambda_3 Q_3 \tag{12.6}$$

Drug can be introduced at the beginning or being drip-fed at a rate $\phi_i$ (for $i = 1$, 2, 3). The parameters $\mu_1 = v_1 k_1$ and $\mu_3 = v_3 k_3$ represent the drug loss rates.

### 12.2.2 Mathematical Model of Anti-quorum Sensing Treatment (in Biofilms)

Now, we consider bacterial cells distribution as a function of space $z$ and time $t$. $z$ is a perpendicular distance from the bacteria biofilm base with $z = H(t)$. $M$ represents a volume fraction, which is occupied by death cells. The rest of the space is captured by EPS (E) and water (W). Thus $N_T + M + E + W = 1$. The pore space is increasing at the time of EPS production. So we get $W = W_0 + \theta E$ where $\theta$ and $W_0$ are constant. Finally, we have $N_T + M + (1 + \theta)E = 1 - W_0$. Furthermore, we assume that quorum sensing process regulates the nutrient concentration ($c$) and EPS production. The following set of equations give a detail mathematical framework of anti-quorum sensing treatment in biofilms (see details in Table 12.1) (Anguige et al. 2006; Ward 2008).

**Table 12.1** Model parameters and its description

| Description | Parameter |
|---|---|
| Oxygen consumption constant | $\rho$ |
| Sets minimal death rate | $\tau$ |
| Birth rate oxygen concentration (Half max.) | $c_1$ |
| Death rate oxygen concentration (Half max.) | $c_2$ |
| Dissolved oxygen concentration | $c_{\text{ext}}$ |
| Maximum birth rate | $B_1$ |
| Maximum death rate | $B_2$ |
| Surface autoinducer mass transfer rate | $Q_a$ |
| Diffusion rate of autoinducer | $D_a$ |
| Diffusion rate of species | $D_i$ |
| Diffusion rate of oxygen | $D_c$ |
| Background EPS production rate | $E_0$ |
| Ma. EPS production rate by up-regulated cells | $k_E$ |
| EPS decay rate | $\lambda_E$ |
| Maximum density of cells in biofilms | $\omega$ |
| EPS generated pore space constant | $\theta$ |
| Initial biofilm depth | $H_0$ |
| Void fraction at maximum bacterial packing | $W_0$ |
| Decay rate of quorum sensing inhibitor | $\lambda_i$ |
| Drip rate of quorum sensing inhibitor | $\varphi_i$ |
| Mean $Q_2$ loss in reaction with autoinducer | $v_1$ |
| 1/conc. When quorum sensing inhibitor is 50% effective | $\gamma_1$, $\gamma_3$ |
| Drug loss rate (due to quorum sensing inhibitor action) | $\mu_2$ |
| Drug loss rate (due to quorum sensing inhibitor action) | $\mu_1$, $\mu_3$ |
| Autoinducer loss rate by LasR/Autoinducer binding | $\sigma$ |
| Autoinducer decay rate | $\lambda$ |
| Autoinducer production rate by down-regulated cells | $k_d$ |
| Autoinducer production rate by up-regulated cells | $k_u$ |
| Down-regulation rate | $\beta$ |
| Maximal up-regulation rate | $\alpha$ |
| Cell birth rate | $r$ |

$$\frac{\partial N_T}{\partial t} + \frac{\partial v N_T}{\partial z} = N_T \left( F_b(c) - F_d(c) \right) \tag{12.7}$$

$$\frac{\partial M}{\partial t} + \frac{\partial v M}{\partial z} = N_T F_d(c) \tag{12.8}$$

$$\frac{\partial N_u}{\partial t} + \frac{\partial v N_u}{\partial z} = \frac{\alpha A}{1+\gamma_1 Q_1} N_d - \beta N_u \tag{12.9}$$

$$\frac{\partial E}{\partial t} + \frac{\partial v E}{\partial z} = \left(E_0 N_T + k_E N_u\right) F_b\left(c\right) - \lambda_E E \tag{12.10}$$

$$0 = D_a \frac{\partial^2 A}{\partial z^2} + \frac{k_u^*}{1+\gamma_3 Q_3} N_u + k_d^* N_T - \frac{\sigma^* A}{1+\gamma_1 Q_1} N_T - \lambda A - \mu_2 Q_2 A \tag{12.11}$$

$$0 = D_1 \frac{\partial^2 Q_1}{\partial z^2} - \frac{\mu_1^* Q_1}{1+\gamma_1 Q_1} N_T - \lambda_1 Q_1 \tag{12.12}$$

$$0 = D_2 \frac{\partial}{\partial z}\left(W \frac{\partial Q_2}{\partial z}\right) - \mu_2 v_2 A W Q_2 - \lambda_2 W Q_2 \tag{12.13}$$

$$0 = D_3 \frac{\partial^2 Q_3}{\partial z^2} - \frac{\mu_3^* Q_3}{1+\gamma_3 Q_3} N_u - \lambda_3 Q_3 \tag{12.14}$$

$$0 = D_c \frac{\partial^2 c}{\partial z^2} - \rho N_T F_b\left(c\right) \tag{12.15}$$

$$\frac{\partial v}{\partial z} = \frac{1}{1-W_0}\left(N_T F_b\left(c\right) + \left(1+\theta\right)\left(E_0 N_T + k_E N_u\right) F_b\left(c\right) - \lambda_E E\right) \tag{12.16}$$

$$\frac{dH}{dt} = v\left(H,t\right) \tag{12.17}$$

One can stimulate the mathematical model with Michaelis-Menten kinetics $F_b\left(c\right) = B_1 \frac{c}{c_1 + c}$ $F_d\left(c\right) = B_2\left(1 - \tau \frac{c}{c_2 + C}\right)$ where $F_d(c)$ and $F_b(c)$ represent bacterial death and birth rate respectively (Ward 2008).

### 12.2.3 Model Predictions

- Up-regulation occurs after the initial period. We observe rapid up-regulation after a certain time (around 3 h) and 12–13% up-regulated cells at any time. Up-regulation bacteria are dependent on the growth phase (in batch culture) (Ward 2008).

- Bacterial colony virulence can be measured by

$$N_u^{\text{frac}} = 1 - \frac{\sigma(\beta + r)}{\alpha k_u} \left(\text{for exponential growth phase}\right)$$

$$N_u^{\text{frac}} = 1 - \frac{\beta(\sigma K + \lambda)}{\alpha k_u K} \left(\text{for stationary phase}\right)\left(K \text{is the population size}\right)\left(\text{Ward 2008}\right)$$

- Anti-LasI agent is the effective treatment than others. Anti-LasR treatment is the most effective QSI (Ward 2008).
- Bacterial biofilm is slowed down after the initial acceleration of growth. Up-regulated cell fraction $U(t) = \frac{\int_0^H N_u(z,t)\,dz}{\int_0^H N_T(z,t)\,dz}$. Living cells are located near the surface (Ward 2008).
- We find a shift in biofilm growth rates with scale $\mu M$. Anti-LasR and anti-LasI agents are similar (Ward 2008).
- QSI is required for suppressing quorum sensing for biofilms and batch culture (Ward 2008).

## 12.3 Nanofabrication

Bacteriology and nanotechnology are the rapidly growing research field. It has been evidenced that bacteria experience spatial structure in different scales. Microfluidic devise and nanofabrication are useful for those scales. We uncover several long-standing questions using nanofabrication, which includes bacterial growth, development, density-dependent behaviour any many more. Bacteria can also grow in a nanofabricated chamber. Dynamics of a bacterial community can be explored by nanofabrication and microfluids (i.e. synthetic ecosystems). Moreover, we can study the completion and cooperation in bacteria communities and shed a new light into the dark matter of biology (Hol and Dekker 2014).

## 12.4 Significant and Fundamental Experimental Observations

- We can find the anti-quorum sensing compounds in six different plants such as *Conocarpus erectus* L., *Quercus virginiana* Mill., *Callistemon viminalis* G. Don, *Bucida burceras* L., *Chamaecyce hypericifolia* (L.) Millsp. and *Tetrazygia bicolor* (Mill.) Cogn. (Adonizio et al. 2006).

- Biofilm formation is regulated by quorum sensing, which is a fundamental cause of urinary tract infection. Curcumin (anti-quorum sensing agent) from *Curcuma longa* inhibit *E. coli* and *P. aeruginosa* biofilm formation (Packiavathy et al. 2014).
- Anti-quorum sensing activity is exhibited by malabaricone C (Chong et al. 2011).
- Quorum sensing inhibitors (QSI) play a crucial role in the biofilm formation. This quorum sensing inhibitors (QSI) are important anti-biofilm agents (Brackman and Coenye 2015).
- Quorum sensing blocker is an important strategy to switch off virulence factor (Finch et al. 1998).
- Essential oils are potential inhibitor of quorum sensing process and prevent biofilm formation (Kerekes et al. 2013).
- *Kigelia africana* extracts have anti-quorum sensing potential (Chenia 2013).
- Diterpene phytol has anti-quorum sensing activity, which reduces *P. aeruginosa* biofilm formation (Pejin et al. 2015).
- *P. aeruginosa* virulence activity can be blocked by small molecules in MvfR communication process (Starkey et al. 2014).
- Punicalagin has anti-quorum sensing potential (Li et al. 2014).
- Parthenolide is a potential anti-biofilm and anti-quorum agent (Kalia et al. 2018).
- A time-sharing behaviour (nutrient competition) is observed between biofilms (Liu et al. 2017).
- *B. cereus* is a quorum sensing and opportunistic human pathogen bacteria. A set of synthetic peptides are discovered, which are potential anti-virulence agents. We can find out several anti-virulence agents using single and multiple amino acid replacements method (Yehuda et al. 2019).

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