One-dimensional reaction-diffusion model for intra- and inter-biofilm oscillatory dynamics

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Abstract

Biofilm is a self-assembling microbial community that can serve as a model system for studying emergent collective dynamics of living systems. *Bacillus subtilis* biofilms resolve a conflict between interior and peripheral cells by electrical signaling and oscillatory colony-growth dynamics. Intriguingly, this dynamics maintain the interior-cell populations within a biofilm, which ultimately improves the survivability against antibacterial treatments as a whole. Beyond intra-biofilm coordination, two biofilms in a microfluidic device can coordinate their oscillatory phases according to the nutrient availability, through which biofilms improve their survivability by effectively utilizing limited resources. While models that can separately simulate intra- and inter- biofilm oscillatory dynamics have been proposed, recapturing these dynamics by a simple phenomenological model remains to be done. Extending from our previous work where we developed a simple reaction-diffusion model that captures the essence of the oscillatory colony growth dynamics of a single biofilm, here we show that a model similar to our previous one can recapitulate the inter- as well as intra-biofilm dynamics.

Biofilms, structured communities of microbes, can be found on almost everywhere -from riverbed stones to kitchen sinks.

It is well known that cells in a biofilm can survive better in harsh environments, such as nutrient limitations and antimicrobial attacks, through their close interactions and their self-organized dynamics. The potential benefits of understanding the mechanisms underlying the high survivability of biofilms are vast, in multitude of research fields. For example, in medical sector, it may prevent prevalence of resistant bacteria which often causes human death (Dufour et al. (2010)). It can also help to develop new bio-inspired design principles for engineering and social systems that can adapt to unpredictable circumstances (Nadell et al. (2008)). Furthermore, it benefits the artificial intelligence and artificial life community because it provides a novel design for intelligent lifelike systems.

In this work, we focus on the oscillatory expansion dynamics of *B. subtilis* biofilm, which has been shown to give rise to a collective high survivability against antimicrobial treatments and nutrient limitations (Liu et al. (2015)). More specifically, under nutrient limitations, biofilm oscillation prevents the interior cells from starving and improves the survivability of biofilms as a whole when exposed to antimicrobial chemicals. Furthermore, two biofilms in a microfluidic device can allow time sharing of limited nutrients between colonies, allowing effective growth of the community (Liu et al. (2017)). These studies illustrate that the biofilm oscillatory dynamics enables utilizing limited nutrient resources and enhance the survivability both at inter- and intra-biofilm levels.

In previous studies, models which can recapitulate the intra-biofilm dynamics (Martinez-Corral et al. (2019); Prindle et al. (2015); Liu et al. (2015)) and the inter-biofilm dynamics (Liu et al. (2017)) have been developed. In a previous study, we reported that a simple and abstract mathematical model using a set of reaction-diffusion equations can successfully recapitulate the intra-biofilm oscillatory growth dynamics (Mikami et al. (2019)). However, whether this model can also recapitulate the inter-biofilm dynamics was unclear. Building on our previous success, here we report that our model, with a slight revision, can indeed recapitulate the inter-biofilm oscillation dynamics.

As reported in our previous work (Mikami et al. (2019)), we introduced three core elements of the biofilm oscillation: bacterial density $v(r,t)$, nutrient $u(r,t)$ and electrical signal $z(r,t)$. Electrical signalling is mediated by potassium waves, which depolarize cells and consequently suppress the nutrient uptake (Prindle et al., (2015)). Since the biofilm expanded to radial directions almost equally (Liu et al., (2015)), one-dimensional model was considered. In this paper, we made a slight modification which did not influence recapitulating the intra-biofilm dynamics. The time evolutions of each elements are described by the reaction-diffusion equations as follows:

$$\dot{v}(r,t) = -k_v v + D_v \cdot \nabla^2 v + k_f v \cdot f(k_1(u - k_2 z - \beta)), \quad (1)$$

$$\dot{u}(r,t) = -k_u u + D_u \cdot \nabla^2 u + u_{in} - k_f v \cdot f(k_1(u - k_2 z - \beta)), \quad (2)$$

$$\dot{z}(r,t) = -k_z z + D_z \cdot \nabla^2 z + k_{vz} v(1 - f(k_h(u - \alpha))), \quad (3)$$

where $k_v, k_u, k_z, k_f, k_1, k_2, k_{vz}, k_h, \alpha$, and β are positive constants, D_v, D_u, and D_z denote the diffusion coefficients. u_{in} denotes an external input. The function f denotes a

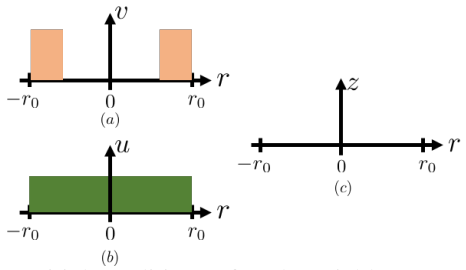

Figure 1: Initial conditions of each variables. (a) Cell density $v(r, 0)$. (b) Nutrient $u(r, 0)$. (c) Electrical signal $z(r, 0)$.

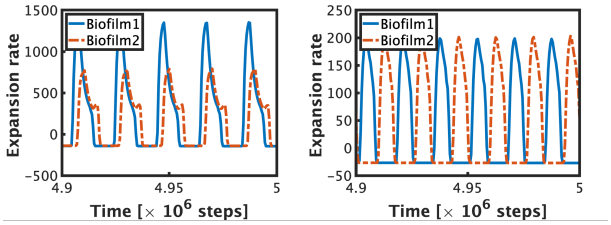

Figure 2: The phase synchronization of expanding rate between two biofilms. The expanding rate of Biofilm 1 and 2 were calculated as the total amount of $v(r, t)$ for negative and positive r, respectively. (a) In-phase synchronization under plenty nutrient ($u_1 = u_0 = 1500.0$). (b) Anti-phase synchronization under poor nutrient ($u_1 = u_0 = 300.0$).

sigmoid-function $f(x) = \frac{1}{1+e^{-x}}$. The first and second terms of Eq.(1)-(3) denote the decay and diffusion, respectively. The third term in Eq.(1) represents the bacterial activities to uptake nutrients from their external environments. This becomes larger with greater nutrient availability $u(r, t)$ and larger cell density $v(r, t)$. Electrical signal $z(r, t)$ has an opposite impact to this term: larger z give rise to smaller values. The fourth term of Eq.(2) shows that $u(r, t)$ decreases due to the uptake of nutrient by cells. The third term of Eq.(3) represents that bacterial cells efflux potassium ions under starvation. This becomes larger with lower nutrient availability $u(r, t)$ and larger cell density $v(r, t)$.

Simulations were performed under the following initial conditions (Fig.1). Two biofilms were initially placed on the both ends of the simulation space, namely,

$$v(r,0) = \begin{cases} v_0 \\ (-r_0 \le r \le (-r_0 + s_0) \cup (r_0 - s_0) \le r \le r_0), \\ 0 \ \ (otherwise), \end{cases} \tag{4}$$

$$u(r,0) = u_0 \ (|r| \le r_0), \tag{5}$$

$$z(r,0) = 0, \tag{6}$$

where v_0, s_0, and u_0 are positive constants. The simulation space was bounded at $r = \pm r_0$, and the Neumann boundary condition was used. To mimic the experimental condition in the previous work (Liu et al., (2015)), an external source of nutrient is given at the center of the simulation space.

$$u_{in} = \begin{cases} u_1 & (r = 0), \\ 0 & (otherwise), \end{cases} \tag{7}$$

where u_1 is a positive constant.

The phase relationship between two biofilms has been shown to converge to in-/anti-phase under higher/lower nutrient availability condition (Liu et al. (2017)). To test whether our model can recapitulate this dynamics, we conducted simulations under two different conditions: $u_1 = u_0 = 1500.0$ and 300.0. Other parameter values were $k_v = 0.0001, k_u = 0.001, k_z = 0.5, k_f = 0.01, k_1 = 1.0, k_2 = 19.0, k_{vz} = 5.5, k_h = 100.0, \alpha = \beta = 210.0, D_v = 7.0 \times 10^{-6}, D_u = 2.33, D_z = 0.23, v_0 = 100.0, s_0 = 10, r_0 = 50, dx = 0.1$, and $dt = 0.001$.

Figure 2 shows the expanding rate of two biofilms when $u_1 = u_0 = 1500.0$ and 300.0. It is found that the two biofilms oscillate and synchronize with in- and anti-phase when $u_1 = u_0 = 1500.0$ and 300.0, respectively. This result agrees with the biological finding (Liu et al. (2017)).

Liu et al. (2017) showed that the synchronization dynamics is influenced by three factors: communication strength between biofilms, externally available nutrient amount, and competition strength between biofilms. The competition strength and the communication strength depend on the cells' capacity for metabolisms and electrical signaling, respectively. In-phase synchronization was shown to be promoted by higher communication strength, smaller competition strength, and larger available nutrient amount, and vice versa. In our model, k_{vz} and u_{in} can be considered to correspond to the communication strength and the available nutrient amount, respectively. The competition strength is not included in our model.

While our model successfully recapitulated the phase dynamics depending on the nutrient amount, the exact mechanism by which in- and anti-phase synchronizations switch depending on the above mentioned factors are still unknown. In future works, we aim to investigate the mechanisms by reproducing the synchronization dynamics depending on the communication strength through more deeply understanding our model.

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