Mechanically-driven spreading of bacterial populations

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A B S T R A C T

The effect of mechanical interactions between cells in the spreading of bacterial populations was investigated in one-dimensional space. A continuum-mechanics approach, comprising cell migration, proliferation, and exclusion processes, was employed to elucidate the dynamics. The consequent nonlinear reaction-diffusion-like equation describes the constitution dynamics of a bacterial population. In this model, bacterial cells were treated as rod-like particles that interact with each other through hard-core repulsion, which introduces the exclusion effect that causes bacterial populations to migrate quickly at high density. The propagation of bacterial density as a traveling wave front over extended times was also analyzed. The analytical and numerical solutions revealed that the front speed was enhanced by the exclusion process, which depended upon the cell-packing fraction. Finally, we qualitatively compared our theoretical results with experimental evidence.

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1. Introduction

In recent decades, much attention has been paid to the collective behavior of bacterial populations. This system is used as the prototype for understanding multicellular assemblies, such as tissue and biofilm [1]. The insight into the underlying mechanism of dynamics is important to biological and medical science.

To cope with unfavorable environmental conditions, bacterial colonies generate varieties of pattern formations [2,3]. The spatiotemporal pattern formation in bacterial colonies results from cell migration and proliferation. These dynamics at a continuum level can be described by reaction-diffusion processes [2–4]. The simplified model [2] relied on a density-dependent (or degenerate) reaction-diffusion equation [5–9], which was an extension of the classical Fisher-KPP equation [10,11]. These well-known solutions [7,8] revealed that bacterial density evolves as a sharp traveling wave with constant front speed [2]. In our previous work, we found an explicit space-time solution for the generalized Fisher-KPP equation in one-dimensional space [12]. This solution evolves from a specific initial condition to a self-similar object that converges to the usual traveling wave on an extended time scale. Although capable of explaining these dynamics, the conventional model omitted the size of the bacterial cell. In real systems, most bacterial cells are rod shaped and grow in dense environments. Accordingly, the mechanical interactions between cells could play crucial roles in the spreading of bacterial colonies.

Recent experimental and theoretical studies showed that mechanical interactions between cells have important roles in the collective behavior of bacterial colonies [13–18]. The dependence on the elastic modulus of the front speed has theoretically been found [19]. It mentions that *the migration of bacteria is caused by cell pushing rather than self-propulsion* in dense colonies [14,17,18]. Therefore, we speculate that the exclusion process that prevents the overlapping of cells could play a crucial role in

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the spreading of bacterial colonies. This issue motivates us to extend the conventional density-dependent reaction-diffusion equation [5–9] by incorporating the cell size into the investigation of the dynamics of bacterial populations.

In this work, we considered the systems of bacterial cells growing on a thin layer of nutrient-rich fluid medium. The bacteria increased in population through cell division and interacted through hard-core repulsion (steric interactions), which resulted in exclusion effects and consequent non-overlapping of cells. Although bacteria are self-propelled particles [20], in colonies of densely packed or non-motile cells, bacterial migration was caused by cell pushing, resulting from cell growth and division, rather than self-propulsion [14,17,18]. Thus, *the bacteria behave similarly as passive particles or non-motile cells* in high density environments. Apart from cells, Bruna and Chapman [21] observed that the self-diffusion of hard spherical Brownian particles in a dilute regime decreased as the density increased, due to the diffusion of any single particle being impeded by collisions with other particles. However, these collisions encouraged the particle to move toward low-density regions, resulting in this biased migration being faster than self-diffusion and enhancing overall collective diffusion. Guided by the work of Bruna and Chapman [21], we propose that bacterial cells move based on hard-core repulsion and without self-propelled motility in dense colonies.

After incorporating exclusion processes in cell (or particle) dynamics, altered diffusion coefficients in the continuum limits were found [22–29]. The enhancement or slowing of diffusion depends upon cell length and the available moving distance, as shown by lattice-based analysis [28]. In some models, diffusion diverges to infinity in closely packed densities [22,23,29]. Singular diffusion has also been modeled through the migration of bacterial biofilm [30,31] and glioblastoma tumors [32]. However, the effect of diverged diffusion on the propagation speed of cell populations remains unknown.

To address this question, we employed a continuum-mechanics approach to cell proliferation [33] in order to investigate the spreading of bacterial populations in the presence of exclusion processes. Additionally, we analytically and numerically elucidated the front speed of bacterial colony expansion in terms of cell size and discussed the consistency of our theoretical results with the experimental evidence.

2. Continuum mechanical model

2.1. Constitution equations

From a macroscopic view, bacterial populations constitute continuum fluid capable of reproducing in order to increase cell numbers. By pushing each other following cell division [14,17,18], population pressure increases as a result of collisions between cells and forces cells to move. During movement, cells encounter friction from the surrounding fluid medium and the substrate surface. For the sake of simplicity, we considered the expansion of bacterial colonies in one-dimensional space, regardless of cell orientation. Adapting from [33], the constitution equations that describe the evolution of the cell density, $\rho(x, t)$, and collective velocity, $V(x, t)$, of the bacterial population at position x and time t are given by

$$\frac{\partial \rho}{\partial t} = -\frac{\partial (\rho V)}{\partial x} + \Gamma(\rho), \tag{1}$$

$$-\gamma V = \frac{\partial p}{\partial x} = \frac{\partial p}{\partial \rho} \frac{\partial \rho}{\partial x}, \tag{2}$$

where $\Gamma(\rho(x, t))$ represents the growth function, $p(\rho(x, t))$ represents the internal population pressure, and γ represents the damping constant. Eq. (1) represents the continuity equation with the growth term. We assume that bacterial growth obeys the law of population growth as described by a logistic function: $\Gamma(\rho) = \kappa \rho (1 - \rho/\rho_m)$, where κ is the rate constant and ρ_m is the maximum density [9,33]. Eq. (2) arises from the force balance between Stokes' law for friction and the pressure gradient, which is similar to Darcy's law describing fluid flow through a porous medium.

We model the bacterial cells as non-overlapping hard-rod particles of average length, σ, that interact through hard-core repulsion. In high-density environments, bacterial self-propulsion can be ignored, since it is dominated by collision between cells. This defines the bacterial cell as a passive particle or non-motile cell that obeys the laws of thermodynamics. For hard-rod fluid in one dimension, the exact pressure is given as

$$p(\rho) = \frac{\rho k_B T}{1 - \sigma \rho}, \tag{3}$$

where k_B is the Boltzmann constant and T represents the temperature [34–36]. In our case where bacterial cells behave as passive particles, the temperature relates to the average translational kinetic energy of a cell, $\langle E_k \rangle = (1/2)k_B T$, we assume that the temperature is constant in our system. The pressure in Eq. (3) diverges to infinity at closely packed density: $\rho \to 1/\sigma$. Notably, in dilute density, $\rho \to 0$, Eq. (3) recovers the pressure of an ideal gas: $p = \rho k_B T$. As shown in [37–39], the pressure for dilute active particles is similar to the ideal gas, except that the source of kinetic energy comes from the swim speed, U_0: $k_B T \propto U_0^2$ [37,38]. As will be shown later, the temperature source is not important; as long as it is constant, the dynamics of our model are invariant.

2.2. Dimensionless equations

We define the maximum density as $\rho_m = 1/\sigma_m$, where σ_m represents the average length occupied by one cell and $\sigma_m > \sigma > 0$. The logistic law limits the growth of bacteria, such that $0 \leq \rho \leq \rho_m < 1/\sigma$. For convenience of further analysis, we