Mechanical reaction-diffusion model for bacterial population dynamics

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The effect of mechanical interaction between cells on the spreading of bacterial population was investigated in one-dimensional space. A nonlinear reaction-diffusion equation has been formulated as a model for this dynamics. In this model, the bacterial cells are treated as the rod-like particles that interact, when contacting each other, through the hard-core repulsion. The repulsion introduces the exclusion process that causes the fast diffusion in bacterial population at high density. The propagation of the bacterial density as the traveling wave front in long time behavior has been analyzed. The analytical result reveals that the front speed is enhanced by the exclusion process—and its value depends on the packing fraction of cell. The numerical solutions of the model have been solved to confirm this prediction.

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In past decades, much attention has paid to the collective behaviors of bacterial populations. To cope with unflavored environmental conditions, the bacterial colonies generate the varieties of pattern formations \cite{1}. This system is used as the prototype for understanding the multicellular assemblies such as tissue and biofilm. The insight into this underlying mechanism is important to biological and medical science.

The reaction-diffusion model, formulated by the nonlinear partial differential equation, has become a theoretical description of the dynamics at continuum level \cite{1–3}. The simplified model \cite{2} relied on the generalization of the classical Fisher-KPP equation \cite{4, 5}, known as the degenerate reaction-diffusion equation (or the density-dependent reaction-diffusion model) \cite{6–10}. From the well known exact solutions \cite{8, 9}, it revealed that the bacterial density evolves as the sharp traveling wave with constant front speed \cite{2}. Although it can explain this dynamics, the conventional model has omitted the size of the bacterial cell. In real systems, the most of bacterial cells have rod shape and grow in dense environments. Accordingly, the direct contact mechanical interaction between cells could play the crucial roles on the spreading of bacterial colony.

The recent experimental results of Refs. \cite{11–14} have shown that the mechanical interaction between cells involves the orientation ordering of cells in the colony. Moreover, the mechanical force involves the transition between two- and three-dimensional growth in the bacterial microcolonies \cite{12–16}. It can mention that the motility of the bacteria is caused by cell pushing rather than self-propelling in dense colony \cite{12, 15, 16}. Therefore, we speculate that the mechanical interaction should drive the expansion of bacterial colony.

In the theoretical studies, the bacterial populations were simulated by the dynamics of elastic rod-like (sphe-
rocylinder) particles with growth and cell division \cite{11–17}. The typical contributed forces in these models consist of elastic repulsion between cells and friction from the surroundings. In Refs. \cite{12–14, 17}, the continuum models were also provided. Interestingly, the dependence on the elastic modulus of the front speed was presented \cite{17}. However, by including the elastic interaction purely, the hard-core repulsion between cells has been omitted in such these models. We argue that this interaction is required because it prevents occupying the same volume of cells. The hard-core repulsion introduces the exclusion process to the system—and it has an important role on the spreading of bacteria in dense colonies.

In contrast to, the discrete models that concern with the exclusion effect have been proposed for studying the cell (or particle) dynamics, with \cite{18} and without proliferation \cite{14, 24}. With proliferation, the population density propagates as the traveling wave \cite{18}. The continuum limits of these models reveal the altered diffusion coefficient of cell by the exclusion effect \cite{19, 24}. Especially, the exclusion process results the fast diffusion in cell migration at high density \cite{19, 20, 24}. The fast diffusion has been also modeled the migration of myxobacteria dense phase \cite{25}, bacterial biofilm \cite{26, 27} and glioblas-toma tumor \cite{28}. However, how the fast diffusion affects the propagation speed of cell populations is unrevealed.

To address this question, in this research, we investigated the spreading of the rod-shaped bacterial population at macroscopic level in one-dimensional space. By incorporating with the hard-core repulsion between cells, a degenerate reaction-fast-diffusion equation has been derived as the constitution dynamics of this system. The aim of this work is to find the expression for the front speed of bacterial colony in the term of cell size parameter, analytically. The analytical results are validated by comparing with the direct numerical solutions of this equation.

We consider the evolution of bacterial density in one-dimensional space, regardless of cell orientation effect.
To derive the governing equations, we adapt the simple continuum mechanics approach for cell population that has been used in Ref. [22]. The bacterial populations are viewed as the continuum fluid that can reproduce to increase the cell numbers by cell division. The bacterial density obeys the continuity equation

\[
\frac{\partial \rho}{\partial t} + \frac{\partial (\rho v)}{\partial x} = \Gamma(\rho), \tag{1}
\]

where \(\rho(x, t)\) is the bacterial density at position \(x\) and time \(t\), \(v(x, t)\) is the collective velocity of the bacterial population and \(\Gamma(\rho)\) describes the growth rate in cell density of bacteria. As usual, we assume that the growth rate obeys the logistic law; that \(\Gamma(\rho) = k \rho (1 - \rho / \rho_m)\), where \(k\) is rate constant and \(\rho_m\) is the maximum density. The logistic law describes the growth of populations under the limited nutrient that the density cannot be greater than the maximum value. Thus 0 \(\leq \rho \leq \rho_m\).

Imagine that, the bacteria are growing in the dense colony on the thin layer of fluid medium, containing nutrient. After separating into two daughter cells, each bacterium pushes the surrounding cells away from its occupied region. This introduces the exclusion effect resulted from the hard-core repulsion that the bacterial cells cannot be overlap. When moving, the cells face the friction from the surrounding fluid medium and the substrate surface. In this scenario, the friction force is formulated by the Stokes’ law that is \(-\gamma v\), where \(\gamma\) is a damping constant. As many as the cell numbers increase by cell division, the local intrinsic pressure \(p(\rho(x))\) increases. Balancing the friction force to the pressure gradient, we obtain

\[-\gamma v = \frac{\partial \rho}{\partial x} = \frac{\partial \rho}{\partial \rho} \frac{\partial \rho}{\partial x}. \tag{2}\]

Eq. (2) is similar to the Darcy’s law that describes the fluid flow in porous media.

We model the bacterial cells as the hard rod particles that interact through the hard-core repulsion. In one-dimensional space, the rod-shaped bacterial cells can be viewed as the non-overlap line segments of average length \(\sigma\). For the hard rod fluid in one dimension, the exact pressure is known

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

where \(k_B\) is Boltzmann constant and \(T\) is temperature [30–32]. Noting that, in one-dimensional space, the density is the cell numbers per unit length and the pressure means force. We assume that the temperature of bacteria system is constant. From Eq. (1), Eq. (2) and Eq. (3), we arise the nonlinear partial differential equation

\[
\frac{\partial \rho}{\partial t} = \frac{\partial}{\partial x} \left[ \frac{\rho k_B T}{\gamma (1 - \sigma \rho)^2} \frac{\partial \rho}{\partial x} \right] + k \rho \left(1 - \frac{\rho}{\rho_m}\right). \tag{4}\]

In Eq. (4), we obtain the altered diffusion coefficient that \(D(\rho) = (k_B T / \gamma) \rho (1 - \sigma \rho)^2\). The factor \(1 / (1 - \sigma \rho)^2\) implies the exclusion effect on the diffusion of bacterial cells. This factor has also appeared in the similar model by different approaches [19, 20, 24]. If the cells have no size (\(\sigma = 0\), Eq. (4) recovers the conventional generalized Fisher-KPP equation [8, 10]; in which the explicit solution in this case has been found in our previous work [33].

The diffusion coefficient goes to infinity as \(\rho \to 1/\sigma\) that causes the cells to migrate extremely fast. The density in this regime means every line segment of average cell length (\(\sigma\)) is occupied by one cell; that is exactly the closed-pack density. To prevent the singularity in diffusion, it suggests that the closed-pack configure is inaccessible; because the bacteria must leave some free space for cell division. That is, we define the maximum density such that \(\rho_m = 1/l_m\) where \(l_m\) is the average length occupied by one cell and \(l_m > \sigma\). Now, we see that the limitation of the bacterial density not only depends on the amount of nutrient but also the exclusion process. We also mention that Eq. (4) looks similar to the cell population models that have been studied in Refs. [25–28]. However, in their model, the cell size parameter (\(\sigma\)) has disappeared.

For convenience in further analysis, we introduce the dimensionless quantities: \(0 \leq u = \rho / \rho_m \leq 1\), \(0 \leq \epsilon = \sigma \rho_m = \sigma / l_m < 1\), \(t' = \alpha t\) and \(x' = [(k \gamma) / (\rho_m k_B T)]^{1/2} x\). Applying these quantities to Eq. (4), we obtain the dimensionless nonlinear reaction-diffusion equation

\[
\frac{\partial u}{\partial t} = \frac{\partial}{\partial x} \left( D(u) \frac{\partial u}{\partial x} \right) + g(u), \tag{5}\]

where \(D(u) = u / (1 - \epsilon u)^2\), \(g(u) = u (1 - u)\) and the prime has been dropped. In one dimension, the packing fraction (\(\epsilon\)) means the length fraction and it is equivalent to the area and volume fraction in two and three dimensions, respectively. Eq. (5) is degenerate in the sense that \(D(0) = 0\), which results the sharp interface between occupied region and cell-free region. It is observed that, as \(0 \ll \epsilon \ll 1\), the diffusion coefficient \(D(u)\) is extremely large when \(u \to 1\). Therefore, Eq. (5) is called a degenerate reaction-fast-diffusion equation.

We focus on the long time behaviour of the system that the population density propagates as the traveling wave: \(u(x, t) = \phi(z)\), where \(z = x - ct\) and \(c\) is the front speed [10]. Substituting the traveling wave solution into Eq. (5), we obtain

\[
\frac{d}{dz} \left( D(\phi) \frac{d\phi}{dz} \right) + c \frac{d\phi}{dz} + g(\phi) = 0. \tag{6}
\]

More general form of Eq. (6) has been analysed previously [44]. In the degenerate reaction-diffusion model, the density must vanish at the finite position, in which \(z^* < \infty\), that undergoes the sharp interface. Then, we consider the density profile that satisfies the following conditions: \(\phi(-\infty) = 1\), \(\phi(z) = 0\) for \(z \geq z^*\), \(\frac{d\phi}{dz} \phi(-\infty) = 0\), and \(\frac{d\phi}{dz} \neq 0\). In addition, for \(\epsilon \in [0, 1]\), \(D(\phi(-\infty)) < \infty\) and \(D(\phi(z)) = 0\) for \(z \geq z^*\).
Multiplying Eq. (6) by $D(\phi)d\phi/dz$ and then integrating with respect to $z$ from $-\infty$ to $z^*$, we obtain

$$c \int_{-\infty}^{z^*} D(\phi) \left( \frac{d\phi}{dz} \right)^2 dz + \int_{-\infty}^{z^*} D(\phi)g(\phi) \frac{d\phi}{dz} dz + \frac{1}{2} \left[ D(\phi) \frac{d\phi}{dz} \right]_{-\infty}^{z^*} = 0. \quad (7)$$

With the density profile conditions, the last term in Eq. (7) vanishes. And then we obtain the front speed $w = D(\phi)\frac{d\phi}{dz}$, and, at $0 < z < z_0$, to the nonlinear reaction-diffusion equation as studied in 3-5. With these known solutions, Eq. (8) into Eq. (5), using $w(\phi) = d\phi/dz$, we can calculate the approximate density profile

$$\phi(z) = \begin{cases} \frac{1}{1 - \exp[b(z-z_0)]}, & z \leq z_0 \\ 0, & z > z_0, \end{cases} \quad (17)$$

where $a = \frac{6\epsilon}{5+2\epsilon}$, $b = \frac{5-4\epsilon}{5\sqrt{2}}$ and $z_0$ is the initial front position that $\phi(z_0) = 0$.

From Eq. (10), we see that the front speed linearly depends on the packing fraction ($\epsilon$) to the correction of $O(\epsilon^2)$. However, we can use the result in Eq. (13) to calculate more precise front speed. Substituting Eq. (13) into Eq. (8), we obtain

$$c \approx \frac{5}{\sqrt{2}\epsilon} \left( (4\epsilon - 6) \ln(1 - \epsilon) + \epsilon^2 - 6\epsilon \right). \quad (18)$$

We see that $c \to \infty$ as $\epsilon \to 1^-$. If we expand Eq. (18) in the series of $\epsilon$, it recovers Eq. (10) at the correction of $O(\epsilon^2)$. It converges to the conventional front speed that $c_0 = 1/\sqrt{2}$ as $\epsilon \to 0^+$. This analytical result shows that the front speed is enhanced by the exclusion process resulting from the hard-core repulsion between cells.

To compare with the analytical results, we solve Eq. (4) directly by using the nonstandard fully implicit finite difference method as used in Ref. 20. The detailed algorithm is described in the Supplemental Material 39. The initial density profile, $u_0(x)$, is set to a step function

$$u_0(x) = \begin{cases} 1, & x < r_0 \\ 0, & x \geq r_0, \end{cases} \quad (19)$$

where $r_0$ is initial front position. Here, we choose that $r_0 = 50$, to ensure that it is far enough from the origin. The front position $r_f(t)$ is the first position that the density falls to zero. Technically, due to the numerical deviation, we measure the first position that the density is less than or equal to $1 \times 10^{-6}$—or $u(r_f, t) \leq 1 \times 10^{-6}$. The front positions are collected for every $t = 1$. The last 50 data points are selected for fitting with the linear equation, $r_f = ct + r_0$, to avoid the transient effect of initial stage. Hence, the slope of this linear equation is equal to the front speed.

The demonstration of the density profile, obtained from the numerical method, is shown in Fig. 1. It is observed that the density profile evolves as the sharp traveling wave with unchanged shape. The front position in a function of time, as shown in Fig. 2, is well fitted with the linear equation as expected. It implies that the density propagates with constant front speed.

\[ w(\phi) = \frac{6}{5\sqrt{2}} (\phi - 1) \left( \frac{5 + 2\epsilon}{6} - \epsilon \phi \right) + O(\epsilon^2) \quad (15) \]

\[ c = \frac{1}{\sqrt{2}} \left( 1 + \frac{2\epsilon}{5} \right) + O(\epsilon^2). \quad (16) \]
TABLE I. The numerical front speed (\(c_{\text{num}}\)) for some selected values of \(\epsilon\).

| \(\epsilon\) | 0.00 | 0.10 | 0.20 | 0.30 | 0.40 | 0.50 | 0.60 | 0.70 | 0.80 | 0.90 | 0.95 | 0.99 |
|----------------|------|------|------|------|------|------|------|------|------|------|------|------|
| \(c_{\text{num}}\) | 0.7074 | 0.7375 | 0.7719 | 0.8124 | 0.8603 | 0.9190 | 1.0934 | 1.2404 | 1.5028 | 1.7713 | 2.3649 |

FIG. 1. (Color online) The demonstration of density profile, \(u(x,t)\), that is obtained by using the numerical method for \(\epsilon = 0.99\) from \(t = 0\) to \(t = 80\). The dashed line is initial density profile. The data are shown for every \(t = 8\).

FIG. 2. (Color online) The demonstration of the front position versus time of numerical density profile for \(\epsilon = 0.99\) from \(t = 0\) to \(t = 80\). The markers are numerical values and the solid linear is the fitting linear equation for the last 50 data points. \(R^2\) is the correlation coefficient.

The front speed by varying some selected values of \(\epsilon\) is show in Table I. The numerical front speed in Table I and the analytical curve generated from Eq. (18) are also plotted in Fig. 3. It shows that the front speed is finite for a given packing fraction that \(0 \leq \epsilon < 1\). Its value increases rapidly as the packing fraction approaches 1.

Only for \(\epsilon = 0\), we have the exact front speed value that is \(c_0 = 1/\sqrt{2} = 0.7071\) \[8–10, 35\]. From our numerical results, the front speed for \(\epsilon = 0\) is 0.7074 that shows the error about 0.04% of the exact value. In Fig. 3, we see that the analytical results are quite in agreement with the numerical results for the small of value of packing fraction \((\epsilon \ll 1)\). Because, the correction of our analytical solution is only first order.

FIG. 3. (Color online) The front speed of varying \(\epsilon\). The solid line represents the analytical curve generated from Eq. (18) and the circle markers represent the selected numerical results.

This theoretical study has demonstrated the effect of mechanical interaction on the spreading of the bacterial populations. In dense colony, the motility of the bacteria is dominated by the hard-core repulsion between cells that results the exclusion process. The exclusion process drives the fast diffusion of bacterial cells at high density. Combining with the growth process, the dynamics of bacterial population can be described by a degenerate reaction-fast-diffusion equation. The propagation of bacterial density in the form of the traveling wave has been analyzed in one-dimensional space. The analytical results reveal that the front speed depends on the packing fraction—and it increases dramatically as this fraction approaches one. This prediction is in agreement with the numerical result, at least for the small value of packing fraction.

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Mechanical reaction-diffusion model for bacterial population dynamics: Supplemental material

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I. THE PERTURBATION SOLUTIONS

The solutions of equation (13) in the main text have been known \cite{1-4}

\begin{align}
  w_0 &= \frac{1}{\sqrt{2}}(\phi - 1), \quad (I.1) \\
  c_0 &= \frac{1}{\sqrt{2}}. \quad (I.2)
\end{align}

Substituting Eq. (I.1) and Eq. (I.2) into equation (14) in the main text, we obtain

\[ \phi(\phi - 1) \frac{dw_1}{d\phi} + (3\phi - 1) w_1 + 3\sqrt{2}\phi^3 - 5\sqrt{2}\phi^2 + (2\sqrt{2} + c_1)\phi - c_1 = 0, \quad (I.3) \]

which is the linear first order ordinary differential equation. After using the integrating factor for solving Eq. (I.3) \cite{5}, we obtain its solution

\begin{align}
  w_1(\phi) &= \frac{1}{(\phi - 1)^2} \left[ \frac{C}{\phi} - \frac{3\sqrt{2}}{5} \phi^4 + 2\sqrt{2}\phi^3 \\
  &\quad - \left( \frac{c_1}{3} + \frac{7\sqrt{2}}{3} \right) \phi^2 + (c_1 + \sqrt{2}) \phi - c_1 \right] \quad (I.4)
\end{align}

where \( C \) is integral constant. To prevent the singularity at \( \phi = 0 \) and \( \phi = 1 \), we require that \( C = 0 \) and \(-3\sqrt{2} + 2\sqrt{2} - \left( \frac{c_1}{3} + \frac{7\sqrt{2}}{3} \right) + (c_1 + \sqrt{2}) - c_1 = 0 \). Thus we obtain

\[ c_1 = \frac{2}{5\sqrt{2}}. \quad (I.5) \]

Substituting Eq. (I.5) into Eq. (I.4), after doing some algebra, we obtain

\[ w_1(\phi) = -\frac{2}{5\sqrt{2}}(\phi - 1)(3\phi - 1). \quad (I.6) \]

II. NUMERICAL METHOD

In equation (5) in the main text, the value of diffusion coefficient increases as the density increases. It is inefficient by solving with the explicit finite difference scheme \cite{6}. Unfortunately, solving with the standard implicit numerical scheme is also difficult because of the factor \( 1/(1-cu)^2 \). We have found that the simplest algorithm that overcomes these obstructions is the non-standard fully implicit finite difference method as used in Ref. \cite{6}.

First of all, we define the discrete density as \( u_j^n = u(x_j, t_n) \) where \( x_j = j\delta x, t_n = n\delta t, \delta x \) is spacing step, \( \delta t \) is time step, \( j \in [0, M], n \in [0, N] \), and \( M \) and \( N \) are integer. Then, we rewrite equation (5) in the main text

\[ \frac{\partial u_j^{n+1}}{\partial t} \approx \frac{\partial}{\partial x} \left( D_j^n \frac{\partial u_j^{n+1}}{\partial x} \right) + f_j^n u_j^{n+1}, \quad (II.1) \]

where \( D_j^n = D(u_j^n) = u_j^n/(1-cu_j^n)^2 \) and \( f_j^n = 1-u_j^n \). Using the standard discretized scheme for the differential operators, we obtain

\[ \frac{u_j^{n+1} - u_j^n}{\delta t} \approx \frac{1}{\delta x} \left[ D_{j+1/2}^{-n} \frac{\partial}{\partial x} u_{j+1/2}^{n+1} \\
  - D_{j-1/2}^{-n} \frac{\partial}{\partial x} u_{j-1/2}^{n+1} \right] + f_j^n u_j^{n+1}. \quad (II.2) \]

We discretize further for the remain gradient terms in Eq. (II.2) and then we have

\[ \frac{u_j^{n+1} - u_j^n}{\delta t} \approx \frac{1}{(\delta x)^2} \left[ D_{j+1/2}^{-n} (u_{j+1/2}^{n+1} - u_j^{n+1}) \\
  - D_{j-1/2}^{-n} (u_{j-1/2}^{n+1} - u_j^{n+1}) \right] + f_j^n u_j^{n+1}. \quad (II.3) \]

The diffusion coefficient at the mid-grid can be computed by

\[ D_{j-1/2}^{-n} = \frac{1}{2} \left( D_{j-1}^{-n} + D_j^n \right), \quad (II.4) \]

\[ D_{j+1/2}^{-n} = \frac{1}{2} \left( D_j^n + D_{j+1}^{-n} \right). \quad (II.5) \]

Noting that the correction of Eq. (II.3) is \( O(\delta t, (\delta x)^2) \). After rearranging Eq. (II.3), we have

\[ \alpha_j^n u_{j-1}^{n+1} + \theta_j^n u_{j+1}^{n+1} + \beta_j^n u_j^{n+1} = u_j^n, \quad (II.6) \]

where

\[ \alpha_j^n = -\mu D_{j-1/2}^{-n}, \quad \beta_j^n = -\mu D_{j+1/2}^{-n}, \quad \theta_j^n = 1 - \delta t f_j^n + \mu \left( D_{j-1/2}^{-n} D_{j+1/2}^{-n} \right), \]

\[ \mu = \delta t / (\delta x)^2. \quad (II.7) \]
We impose the zero flux condition at the boundary grid, saying Ω, that \( \frac{\partial u}{\partial x} |_{\Omega} = 0 \) or \( \frac{u_{n+1}^n - u_n^n}{2\delta x} = 0 \). Consequently, \( u_{i-1}^n = u_{i+1}^n \) and \( D_{n+1}^n = D_{n+1/2}^n \). Then, we rewrite Eq. (II.6), subjected to the zero flux boundary condition, in the matrix form

\[
A^n \cdot U^{n+1} = U^n, \quad \text{(II.8)}
\]

where

\[
A^n = \begin{bmatrix}
\theta_0^n & 2\beta_0^n & \cdots & \cdots & 0 \\
\alpha_1^n & \theta_1^n & \beta_1^n & \cdots & \vdots \\
\vdots & \ddots & \ddots & \ddots & \vdots \\
\vdots & & \alpha_{M-1}^n & \theta_{M-1}^n & \beta_{M-1}^n \\
0 & \cdots & \cdots & 2\alpha_M^n & \theta_M^n
\end{bmatrix}, \quad \text{(II.9)}
\]

and

\[
U^n = \begin{bmatrix} u_0^n & u_1^n & u_2^n & \cdots & u_M^n \end{bmatrix}^T. \quad \text{(II.10)}
\]

According to the boundary condition, \( \theta_0^n = 1 - \delta t f_0^n + 2\mu D_{n+1/2}^n \) and \( \theta_M^n = 1 - \delta t f_M^n + 2\mu D_{n-1/2}^n \). The numerical density can be obtained by solving the matrix equation (Eq. (II.8)) iteratively.

To find the stability condition of this numerical scheme, we use the von Neumann solution

\[
u_j^n = (\lambda)^n e^{ikj\delta x}, \quad \text{(II.11)}
\]

where \( \lambda \) is amplification factor and \( k \) is wave number. Substituting Eq. (II.11) into Eq. (II.3), we obtain

\[
\lambda = \left[ 1 - \delta t f^n_j - \mu D_{j+1/2}^n (e^{ik\delta x} - 1) + \mu D_{j-1/2}^n (1 - e^{-ik\delta x}) \right]^{-1}. \quad \text{(II.12)}
\]

For stable and temporal non-oscillated numerical solution, it requires that \( 0 < \lambda \leq 1 \). According to the fact that \( 0 \leq f_j^n \leq 1 \) and \( 0 \leq D_j^n < \infty \), without the reaction term \( (f^n_j) \), this algorithm is unconditional stable as long as \( \delta x \ll 1 \). With term reaction term, solution slowly grows to the finite value as long as \( \delta t \ll 1 \). As proved in Eq. (II.12), this algorithm is quite stable for this kind of problem.

In our computation, we choose the spacing step and the time step, respectively, such that \( \delta x = 0.05 \) and \( \delta t = 0.01 \). The computations are performed on 3,000 grids for \( \epsilon \in [0, 0.5] \) and on 5,000 grids for \( \epsilon \in (0.5, 1) \) with 8,000 iterations.

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