込み合いによる細胞の極性と運動の秩序促進

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概要

本研究では細胞の集団運動での込み合い効果を単分散性の反発相互作用セルラー Potts 模型で調べた. 細胞が疎な場合と比較すると, 込み合った細胞では集団運動を起こす推進力閾値が大きく下がることが分かった. この結果から, 込み合いにより細胞は極性秩序を促進し, 集団運動を行うと言える.

Crowding-Boosting Polarity and Motion Order of Cells

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Abstract

We investigate the crowding effect in a collective cell motion in the cellular Potts model with the monodispersity and repulsive interaction. In comparison with scattered cells, the threshold propulsion of crowding cells for forming a collective motion is largely reduced. We suggest that the crowding boosts the polarity order and stabilizes the collective cell motion.

1 Introduction

Collective motions of eukaryotic cells with a directional order often appear in organogensis [1]. The collective motions are stable even in fluctuations of their shapes and surrounding tissues. A possible stabilizer of the collective motions is a crowding effect of cells. For example, the collective motion is stabilized by the exclude volume interaction of crowding cells, which suppresses random motions. This stabilization mechanism essentially differs from that in the Vicsek-type model without the exclude volume [2] and has been not sufficiently explored.

In the exploration, there exists the issue that the crowding effect on the collective cell motions cannot simply be distinguished from other effects, which also promotes the collective motions. For example, the effect has not been clearly distinguished from the polarity memory effect [3,4]. In addition, the crowding effect is canceled by the jamming in the case of polydisperse crowding cells [5,6]. In experimental investigations, we should carefully control states of cells, while healthy eukaryotic cells are empirically known to have monodispersity. Instead of this experiment, the present work theoretically realizes a tractable model of cells in a computer and thereby aims to examine the crowding effect.

In the present paper, we investigate a collective motion of crowding cells based on the cellular Potts model [7]. We consider a range of propulsion less than the fluctuation energy scale in order to avoid the alignment effect of the polarity memory. In addition, we employ an ideal monodisperse system to avoid jamming states. We compare the motion and configuration between the scattered and crowding cells. We show that the crowding boosts the polarity order and stabilizes the collective motion.

2 Model

We employ the cellular Potts model with low propulsion for the comparison between the scattered and crowding cases. The dynamics of cells in this model represents the dynamics of Potts states $\{m(\boldsymbol{r})\}$ in the monte carlo simulation. Here, $\boldsymbol{r}$ is a site of a square lattice with the linear size L. $m(\boldsymbol{r})$ is a number in $\{0, 1, 2, \ldots, N\}$. For $m(\boldsymbol{r}) \neq 0$, $\boldsymbol{r}$ is occupied by the $m(\boldsymbol{r})$-th cell. For $m(\boldsymbol{r}) = 0$, $\boldsymbol{r}$ is empty. The total number of cells, N, is fixed to a certain number. Hamiltonian of the state is

$$\mathcal{H} = \mathcal{H}_S + \mathcal{H}_B + \mathcal{H}_P. \tag{1}$$

The first term in Eq. (1) is the surface free energy

$$\begin{aligned}\mathcal{H}_S = \gamma_{\mathrm{C}} \sum_{\boldsymbol{r}\boldsymbol{r}'} \eta_{m(\boldsymbol{r})m(\boldsymbol{r}')}\eta_{0m(\boldsymbol{r}')}\eta_{m(\boldsymbol{r})0} \\ + \gamma_{\mathrm{E}} \sum_{\boldsymbol{r}\boldsymbol{r}'} \eta_{m(\boldsymbol{r})m(\boldsymbol{r}')} \left[\delta_{0m(\boldsymbol{r}')} + \delta_{m(\boldsymbol{r})0}\right],\end{aligned} \tag{2}$$

where γ_{C} is the surface tension between cells, γ_{E} is that between cells and the empty space. η_{nm} is $1-\delta_{nm}$ and δ_{nm} is the Kronecker δ. The summation of the site pairs between $\boldsymbol{r}$ and $\boldsymbol{r}'$ is taken over the nearest and next nearest sites.

The second term is the Bulk free energy,

$$\mathcal{H}_B = \kappa \sum_m (1 - \frac{\sum_{\boldsymbol{r}} \delta_{mm(\boldsymbol{r})}}{A})^2, \tag{3}$$

where κ is the bulk modulus and A is the reference occupation area. A is common for all cells to inhibit jamming states due to the polydispersity.

The third term is the propulsion energy [4, 8]

$$\mathcal{H}_P = -\varepsilon \sum_m \sum_{\boldsymbol{r}\in\Omega_m} \boldsymbol{p}_m \cdot \boldsymbol{e}_m(\boldsymbol{r}). \tag{4}$$

It expresses the persistent motions of cells by collaborating with the equation of the unit vector $\boldsymbol{p}_m$ that is the polarity of mth cell [9–11],

$$\frac{d\boldsymbol{p}_m}{dt} = \frac{1}{\tau}\left[\frac{d\boldsymbol{R}_m}{dt} - \left(\frac{d\boldsymbol{R}_m}{dt}\cdot \boldsymbol{p}_m\right)\boldsymbol{p}_m\right]. \tag{5}$$

Here, ε is the propulsion, Ω_m is the set of sites occupied by the mth cell, $\boldsymbol{e}_m(\boldsymbol{r})$ is a unit vector indicating from $\boldsymbol{R}_m$ to $\boldsymbol{r}$, τ is the ratio of $d\boldsymbol{R}_m/dt$ to $d\boldsymbol{p}_m/dt$, where $\boldsymbol{R}_m$ is the center of the mth cell as a parameter of propulsion. $\boldsymbol{R}_m$ is quasistatically equal to $\sum_{\boldsymbol{r}\in\Omega_m} \boldsymbol{r} / \sum_{\boldsymbol{r}\in\Omega_m}$.

The monte carlo Monte Carlo procedure based on $\mathcal{H}$ is constructed as follows: the monte carlo Monte Carlo step (mcs) consists of L^2 single flips. In the single flip, the copy of a Potts state is attempted to randomly chosen site $\boldsymbol{r}$ from its randomly chosen nearest or next nearest site. The copy is accepted with Metropolis probability with an inverse temperature β [7]. In single mcs, $\boldsymbol{p}_m$ and $\boldsymbol{R}_m$ are fixed with the assumption that they are slow variables. $\boldsymbol{p}_m$ and $\boldsymbol{R}_m$ are updated once between each two consecutive mcs by Eq. (5) and $\boldsymbol{R}_m = \sum_{\boldsymbol{r}\in\Omega_m} \boldsymbol{r} / \sum_{\boldsymbol{r}\in\Omega_m}$, respectively.

In this simulation, we employ the system with $L = 196$ and $A = 64$. We impose the periodic boundary condition to enable us to avoid the vortex or jamming due to complex confined boundary condition [6]. We choose $N = 256$, 324 for scattered cases and $N = 529$ for crowding case. These values correspond to the area fractions of $\phi = NA/L^2 = 43\%$, 54% and 88%, respectively. The latter is above the random close packing fraction of $\phi \simeq 84\%$ [12] and is near the value used in the previous work [6]. We consider the parameters $\beta = 0.5$, $\kappa = 0.3 \times A^2$, $\tau = 20.0$ to realize the cell motion by the flexible deformations of cell shapes. We realize the repulsively interacting cells by $\gamma_{\mathrm{C}} = 5.0$ and $\gamma_{\mathrm{E}} = 2.0$ to exclude the effect of the cell-cell adhesion, which is another factor of the collective motion and thereby complicates our examination.

3 Results and Discussions

To investigate the motion order, we consider the polarity order. Since the polarity order indicates the order of propulsion directions, it is a suitable probe of the motion order [2]. The polarity order is defined by finite values of the order parameter,

$$P = \left| \frac{1}{T}\int_{T_0}^{T} dt \frac{1}{N}\sum_m \boldsymbol{p}_m \right|, \tag{6}$$

where T_0 is the number of mcs for the relaxation of states from an initial state. We choose the initial state where the cells are aligned in a square lattice array with randomly oriented polarities. We em-

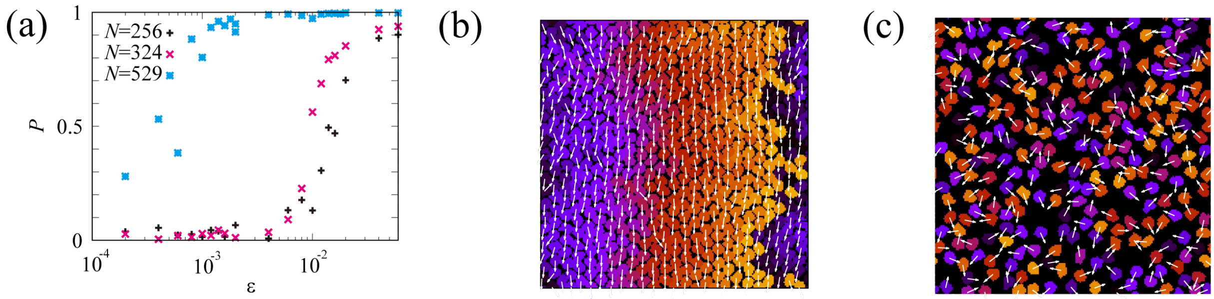

図 1: P as a function of ε for N = 256 (+), N = 324 (×) and N = 529 (∗). The snapshots of states at ε = 0.002 for (b) N = 529 and (c) N = 256. Different color domains are different cells and white arrows at the center of cells are polarities. Black regions are empty space.

ploy $T_0 = 10^5$ empirically. T is the number of mcs for the order parameter calculation. We set $T = 5 \times 10^4$. The value of P takes unity in the motion order and otherwise takes small smaller values.

We employ low values of ε corresponding to cell propulsion less than the shape fluctuation of cells at $\beta^{-1} = 2.0$. This aims to avoid the polarity memory effect that stabilizes the collective cell motion in the strong propulsion [4]. To do this, we firstly calculate the range of ε where the collective motion is absent in the scattered cases (N = 256 and N = 324). Then, we examine the collective motion of crowding cells in this range.

We plotted P as a function of ε for the scattered and crowding cases in Fig. 1(a). The logarithmic plot for the horizontal axis of ε is used for the convenience of data displaying for very low values of ε. For the scattered case, P rapidly increases at threshold values of ε. In this case, the threshold takes a value larger than the order of 10^{-2}. Therefore, we focus on ε lower than the threshold and examine the crowding case. In this range of ε, the threshold value of ε for the crowding case (N = 529) is not clearly observed. For low values of ε, P has finite values down to very small ε's in the order of 10^{-4}. Thus, the threshold value of ε is several ten times smaller than that for N = 256 at least.

Next, we move onto the examination of the cell configuration in order to get insights into the origin of the collective motion for the discussion later. For this purpose, we choose $\varepsilon = 0.002$, where P for the crowding case is almost unity and that for the scattered case is negligibly small. We give snapshots of the cell configurations and their polarities in Figs. 1(b) and 1(c) for N = 529 and N = 256, respectively. For the crowding case in Fig. 1(b), the cells do not only align their polarity in the same direction but also take a near regular lattice configuration. It is contrast with the fluid states of both the degrees of freedom in the scattered case in Fig. 1(c). This suggests that the crowding suppresses the fluctuation and thereby stabilizes the orders in the polarity and configuration.

Hereafter, let us discuss the dependence of P on ε and speculate the underlying mechanism of the orders. This behavior of P as a function of ε is outside the scope of the scaling law for large ε in the previous work [4]. This is because the necessary condition for the collective motion in the previous work is independent of ε. In addition, since ε is less than other energy scales, energy crossover is absent for this range of ε. In the present case, the threshold value of ε is expected to be the simple entropic effect that the directed propulsion is washed out by the isotropic shape fluctuation in Eq. (5). Therefore, the threshold is speculated to be determined by the ratio of ε to β^{-1}, namely $\beta\varepsilon$ and is independent of N. In fact, the threshold values are almost common between N = 256 and N = 324.

On the basis of this speculation, the persistence motion, which is necessary for the collective motion in the previous work [4], is expected to disappear for small $\beta\varepsilon$ below the threshold. In fact, for ε of 0.002 below the threshold, the scattered cells exhibit diffusive behavior $d^2 \simeq t$ in their mean square displacements d^2 in all ranges of the time period t down to 10 mcs in our observation (not shown). The corresponding persistence length of the cell trajectory is negligibly short: the estimated persistence length is at most $10^{-2}a$ with the measured cell velocity of $10^{-3}a$/mcs in the scattered case, where a is the lattice constant.

If the threshold value is determined only by the value of $\beta\varepsilon$, the threshold value for the crowding case is independent of the density. In this case, the threshold is expected to be the similar value of the scattered case at the same value of β. However, the finite values of P down to 10^{-4} are unexpectedly observed. This result implies the crowding effect on this collective motion. Namely, by suppressing the shape fluctuation of cells, the crowding boosts the emergence of the polarity order originally associated with the persistent motion, which disappears in the fluctuation in the scattered case. And finally, it stabilizes the collective motion.

4 Summary and Remarks

In this simulation, we examined the crowding effects in the collective cell motion. Even in low propulsion, the crowding cells form an unexpected collective motion with the emergence of the polarity order. This implies that the crowding naturally boosts the order of polarities and thereby the collective motion. It suggests the hypothesis that, in crowding situations, cells utilize this boosting for stabilizing the collective motion in organogenesis with strategically keeping certain levels of the monodispersity as observed for wild-type cells.

Let us consider the confirmation of the mechanism of the boosting. As mentioned above, the mechanism is expected to be the suppression of the cell shape fluctuation in the crowding cells. Furthermore, since the configuration has a triangular lattice in the snapshot in Fig. 1(b), the suppression may further be enhanced by the lattice formation through the Alder transition in the comoving frame. The confirmation for this suppression is basically possible on the basis of the detail fluctuation analysis of cell configurations and needs further examinations including this analysis in future works.

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