細胞間接触が誘発する単距離秩序のゆらぐ細胞集団運動

松下勝義, 新垣大幸, 藤本仰一

広島大学 数理生命科学プログラム

概要

細胞の集団運動では他の細胞を認識して運動することでその運動を秩序化する. その中に細胞が他の細胞と接触した際に応答して運動する様式があり, 接触誘発と本稿では呼ぶ. この様式では別の様式である相互誘導において起きる運動秩序化を抑制する短距離秩序が現れる. 本研究ではこの短距離秩序の理解ため, 比較的小さいシステムサイズでの有限サイズ効果を利用することを試みた. 特にそのような有限サイズ効果は運動維持性の影響を受けるためその維持性への依存性を調べた. その結果, 運動の秩序が空間的に生まれるものの時間的に大きく揺らぎ続ける状態が現れることが判った.

Fluctuating Collective Cell Motion with Short-Range Order due to Contact Triggering

Katsuyoshi Matsushita, Taiko Arakaki, Koichi Fujimoto

Program of Mathematical and Life Sciences, Hiroshima University

Abstract

Cells utilize their response behavior to mutual contacts to order their motion in their collective movement. Typical response behavior is that the simple mechanical cell contact triggers the motion of the cell. We call this behavior contact triggering. This behavior makes the state have an ordered motion in a short range, which results in the relative instability of the collective movement in comparison with other known behaviors. We investigate this state in a model cell system by using a finite size effect at a small system size. In particular, since the effect is empirically known to depend strongly on the response time of cell polarity in other response behaviors, we examine this dependence in this system. The simulation of this system shows the emergence of motion ordering and large directional fluctuation of the motion.

1 Introduction

Collective movement of cells contributes to organ formation in various biological systems. In the movement, cells mechanically contact each other and show motion ordering. The intercellular interaction for the ordering uses molecular binding bridges between membranes. The binding molecules consist of two types, receptors and ligands [1]. The reception of ligands by receptors drives the motion of the cell that has the receptors. The direction of motion reflects the spatial distribution of these molecules localizing on the cell membrane of edges. Namely, the distributions are a determinant factor for directional changes in cellular motion. This distribution determines the spatial inversion symmetry of the cellular interaction by forming the so-called "cell polarity". The symmetry is expected to contribute to the stability of the ordered motion on the basis of the insights into the active matter physics [2]. Therefore, the molecular distribution is naturally expected to determine the motion ordering.

In the typical spatial distribution, receptors concentrate on one side of the cells and determine the direction of cell motion [3–5]. The distribution due to this one-side concentration is a typical cell polarity for moving cells, and we call this polar distribution. Another type of binding molecule, ligands, can have a variety of their distribution. For example, in the case of homophilic adhesion, a ligand

is identical to the receptor and, trivially, has the same polar distribution in the same cell [6]. Another possible ligand distribution is uniform when the ligand differs from the receptor. We call the mechanism of motion ordering due to polar distribution "mutual guiding". We call that due to uniform distribution "contact triggering". In the former mechanism, the cell can inform surrounding cells of its direction through the direction of the polar distribution of the ligand [7]. In contrast, in the latter case, the cell cannot inform surrounding cells of their direction of motion because of no particular direction in the ligand distribution [8]. The dependence of motion ordering in these two mechanisms is not well clarified.

Our previous work focusing on this dependence showed a relative instability of motion order for the contact triggering [9]. The work calculated the order parameter of the direction of the receptor polar distribution with increasing the driving force. It showed that the increase of the order parameter with the driving force is relatively weak in the contact triggering in contrast to the mutual guiding. This realativly-weak increase in the case of contact triggering implies that the information through the polar distribution of ligands is not necessary but effective for motion ordering. As the explanation of the relatively weak increase, we speculated that the domain of ordered motion in this state remains only in a particularly short range. The examination of this speculation is a crucial issue for us to understand the instability of the ordered motion due to contact triggering.

In the present paper, we investigate the state with ordered motions due to the contact-triggering in order to understand the instability of collective movement. The effects of ordered motions in a short range are invisible based on the order parameter in the simulation of a large system size because the contribution of the domains of the ordered motion to the order parameter is expected to cancel each other. To avoid this invisibility, we consider a small-size system where the domains of ordered motion do not cancel in the contribution to the order parameter. The stability of short-range order in small system sizes is empirically expected to depend on the response time scale of receptor cell polarity τ [10]. Therefore, we calculate the dependence of the order parameter on τ by using the cellular Potts model [11]. We find that the state has a large directional fluctuation of ordered motion over the small system size. This existence of the highly fluctuating direction may be the origin of the relatively weakened cell movement in contact-triggering.

2 Model

Our model is a variant of the cellular Potts model [11]. The model is formulated on a two-dimensional square lattice with a linear size L. The lattice axes of the square lattice are set in the x and y directions. We set the system size L at 96, which is smaller than that in previous work ($L \geq 192$) [9]. As shown later, this small size enables the model cells to stabilize an ordered motion over the system, which is not easily observed in the previous work.

The states in this model consist of the set of Potts states $m(\boldsymbol{r})$ at the square lattice points and the set of a pair of a unit vector $\boldsymbol{p}_n$ and a center position of cells $\boldsymbol{R}_n$ for each nth Potts state. The former set expresses the cell configuration, and the latter pair expresses the directions of polar distribution for receptors of nth cells. The state $m(\boldsymbol{r})$ at $\boldsymbol{r}$ represents the cell index occupying $\boldsymbol{r}$ and takes a number from 0 to the number of cells $N = 144$. Thus, the domain of $m(\boldsymbol{r}) = n$ expresses the shape of nth cell. Exceptionally, $m(r) = 0$ represents the empty space at $\boldsymbol{r}$.

The dynamics of the Potts state is defined as a stochastic copy process with given Hamiltonian $\mathcal{H}(s)$, where s is a state consisting of $\{m(\boldsymbol{r})\}$, $\{(\boldsymbol{p}_n, \boldsymbol{R}_n)\}$. For each copy process, a copy to a randomly chosen site $\boldsymbol{r}$ from its randomly chosen neighboring site $\boldsymbol{r}'$ is accepted by the Metropolis probability $\min[P(s_a)/P(s_b), 1]$. Here, the neighboring sites consist of the nearest and next nearest sites. s_a and s_b are the states after copy and before copy, respectively. $P(s)$ is the realization probability given by the Boltzmann weight $\exp[-\beta\mathcal{H}(s)]$, with a strength of cell shape fluctuation $\beta = 0.5$. $16L^2$ copies constitute 1 Monte Carlo step, which is the unit of time. The Monte Carlo steps generate consecutive state series. For each interval between two Monte Carlo step, p_n is updated by [5, 12, 13]

$$\dot{\boldsymbol{p}}_n = \frac{1}{a\tau}\hat{P}_{\perp \boldsymbol{p}_n}\dot{\boldsymbol{R}}_n. \tag{1}$$

Here, $\hat{P}_{\perp \boldsymbol{p}_n}$ is a projecton operator in the perpendicular direction to $\boldsymbol{p}_n$. The a is lattice constant and set to unity. τ is the response time scale ratio of $\dot{\boldsymbol{p}}_n$ to $\dot{\boldsymbol{R}}_m$. The dependence of the state on τ is examined for motion ordering. The equation is solved by the Euler method with a time difference of 1 Monte Carlo step. $\boldsymbol{R}_n$ is also updated to the center of mass of the nth cell.

The Hamiltonian $\mathcal{H}$ is the sum of adhesion part $\mathcal{H}_a$, the area stiffness part $\mathcal{H}_s$, and the driving part $\mathcal{H}_d$,

$$\mathcal{H}_a = \sum_{\boldsymbol{r}\boldsymbol{r}'} \eta_{m(\boldsymbol{r})m(\boldsymbol{r}')}\gamma(m(\boldsymbol{r})m(\boldsymbol{r}')), \tag{2}$$

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

$$\mathcal{H}_d = -\delta \sum_{\boldsymbol{r}\boldsymbol{r}'} \eta_{m(\boldsymbol{r})m(\boldsymbol{r}')}(\boldsymbol{p}_m(\boldsymbol{r}) \cdot \boldsymbol{e}_m). \tag{4}$$

Here, $\eta_{kl} = 1 - \delta_{kl}$ is the indicator of Potts state domain boundaries and δ_{kl} is the Kronecker delta. The surface tension $\gamma(kl)$ takes 4.0 when the boundary is cell-cell one, namely, $k \neq 0$ and $l \neq 0$. Otherwise, it takes unity. κ and A are the area modulus and the reference area of a cell. δ

is the driving force due to contact triggering and is set to 0.2. In the case of $\delta = 0.2$, cell motions were observed in the previous work [9]. $\boldsymbol{e}_n(\boldsymbol{r})$ is $(\boldsymbol{r} - \boldsymbol{R}_n)/|\boldsymbol{r} - \boldsymbol{R}_n|$.

We obtain a relaxation state from an array of cells with random $\{\boldsymbol{p}_n\}$ through the 10^5 Monte Carlo steps. Then, we calculate the order parameter [14]

$$\boldsymbol{P}(t) = \frac{1}{N}\sum_n \boldsymbol{p}_n(t). \tag{5}$$

Here, we observe this value during $T = 10^5$ Monte Carlo steps. By $\boldsymbol{P}$, we examine the existence of the ordered state.

3 Result

To examine a typical behavior of $\boldsymbol{P}$, we plot the components of $\boldsymbol{P}$, namely P_x and P_y in Fig. 1. In this data, the response time of $\{\boldsymbol{p}_n\}$, τ, is set to 4.0. The components of $\boldsymbol{P}$ highly fluctuate in the simulation. This type of fluctuation is not observed in the case of the mutual guiding mechanism when an ordered motion exists [9]. In addition, the components frequently take values near unity. Therefore, the cell motions form an ordered state, at least for a short time. In contrast to the mutual guiding, intrinsic fluctuation emerges even in the ordered motion in the contact triggering.

This state with the fluctuation is similar to a transition state from solid to fluid states with increasing driving force in the case of self-propelled cells [10]. Therefore, one possible origin of this state is a transition from solid to fluid. We plot it in the same figure to confirm the absence of fluctuation in the absolute value $|\boldsymbol{P}|$ due to the transition. As expected, the value of $|\boldsymbol{P}|$ is almost a constant value near unity, and therefore, the motion direction nearly exhibits a spatially ordered state over cells. The spatial order of motion direction in this state is a similar property of the transition state of self-propelled cells. This similar property may imply that the origin of the fluctuation is the transition from solid to fluid.

In examining the transition state, we also recall that the destabilization effect of the direction of $\boldsymbol{P}$ originates from the short response time [15]. The effect of short response time may be another possible origin of this fluctuating short-range state. To check the possibility of the effect of short response time τ, we calculate the time average value of the order parameter

$$P(\tau) = \left|\frac{1}{T}\int_T dt\boldsymbol{P}(t)\right| \tag{6}$$

as a function of τ. We plot $P(\tau)$ in Fig. 2. $P(\tau)$ in response times shorter than 2 are much lower values and indicate the fluctuating state similar to the state previously observed in the case of self-propelled states [10, 15]. In contrast, the order parameter remains finite for the larger value of τ.

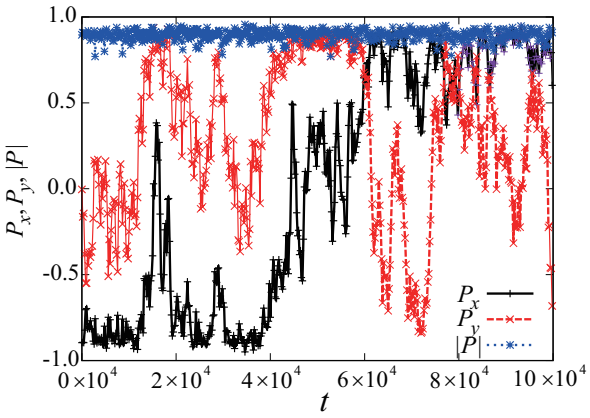

Fig. 1: Components of order parameters $P_x(t)$, $P_y(t)$ and absolute value of the order parameter $|\boldsymbol{P}(t)|$ as a function of Monte Carlo steps t. The origin of time is the end step of the relaxation simulation.

These finite values of the order parameter indicate the emergence of states distinct from that under the effect of a short response time. This state is expected to correspond to the fluctuating state for $\tau = 4.0$ in Fig. 1. The fluctuated characteristics seem to be observed as the non-systematic dependence of $P(\tau)$ on τ. These results indicate that the fluctuating state does not originate from the short response time at least but from the emergence of the ordered motion in a short range with intrinsic fluctuation.

We also plot the collective velocity $v(\tau)$ as a function of τ

$$v(\tau) = \left|\frac{1}{TN}\int_T dt\sum_n \boldsymbol{d}_n(t)\right|, \tag{7}$$

to confirm the contribution of the short-range order state to the collective movement. Here, $\boldsymbol{d}_n(t)$ is the displacement per Monte Carlo step for the nth cell. In Fig. 2, the dependence of $v(\tau)$ on τ is consistent with that of $P(\tau)$ and, hence, the non-systematic behavior is also observed in $v(\tau)$. Therefore, the short-range order reflected in $P(\tau)$ mainly determines the collective velocity in this collective movement.

4 Discussions and Remarks

The present work investigates ordered cell motions in short range with contact-triggering. We find a large directional fluctuation of ordered motion in a small system size, which is not observed for a large system size in previous work [9]. The domains of the motion order with directional fluctuation in the large system size are expected to have different directions of motion and, thereby, cancel each other in the contribution to the order

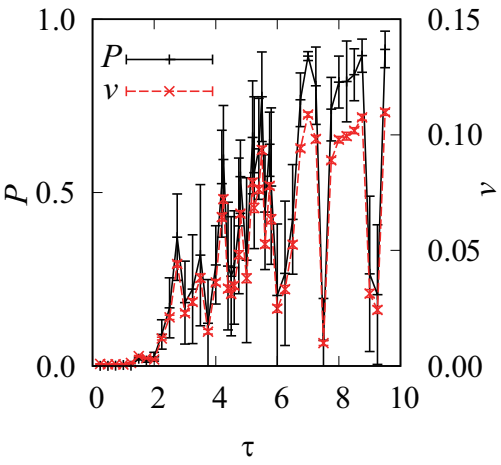

Fig. 2: $P(\tau)$ as a function of the time ratio τ proportional to the response time.

parameter. The observation of the directional fluctuation implies that the emergence of the direction fluctuation is the origin of the relative instability of the collective movement for contact triggering in contrast with mutual guiding. The fluctuation is expected to result from the transition state from solid to fluid.

The comparison of this state with states in other systems may provide additional insights into this state. The fluctuation in this state is not observed so far in the states of mutually guiding cells[7, 16, 17]. Moreover, the comparison with the mutual guiding indicates that the information transfer of the motion direction through the polarized ligand distribution contributes to the stability of the collective movement. In fact, the mutual guiding in the small system size does not show the non-systematic dependence of $P(\tau)$ (not shown here).

The physical mechanism originating the difference in the stability between contact-triggering and mutual guiding is not fully understood yet. The hint for us to approach the difference may be the previous observation of cell array formation in the case of the mutual guiding [13]. The array formation is expected to correlate highly with the alignment of the cellular motion direction. Furthermore, the array formation is not expected for contact-triggering. From these hints, we hypothesize that the stability difference between these mechanisms may originate from the difference between cell configurations. Namely the cell array formation inhibits the fluctuating transition state in the case of the mutual guiding.

Now, the large system-size simulations do not provide evidence for the array formation of mutual guiding. The observation difficulty of this array originates from the visible condition that the arrays are only observable for marginal cell densities between individual and collective movements [13]. Instead of directly observing these arrays, we speculate that the array formation is observable in a finite-size effect of a small-size system, the size of which is comparable with the array size. If this speculation is true, a small-size simulation may be effective in the observation of these arrays. We should examine in the future to solve this mechanism of stability difference.

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References

[1] U. S. Schwarz and S. A. Safran, Rev. Mod. Phys. **85**, 1327 (2013).

[2] M. C. Marchetti, J. F. Joanny, S. Ramaswamy, T. B. Liverpool, J. Prost, M. Rao, and R. A. Simha, Rev. Mod. Phys. **85**, 1143 (2013).

[3] J. C. Coates and A. J. Harwood, J. Cell Sci. **114**, 4349 (2001).

[4] C.-H. Siu, T. J. C. Harris, and E. W. Jun Wang, Semin. Cell. Dev. Biol. **15**, 633 (2004).

[5] B. Szabó, G. J. Szollosi, B. Gonci, Z. Juranyi, D. Selmeczi, and T. Vicsek, Phys. Rev. E **74**, 061908 (2006).

[6] M. Takeichi, Nat. Rev. Mol. Cell. Biol. **15**, 397 (2014).

[7] K. Matsushita, Phys. Rev. E **97**, 042413 (2018).

[8] K. Matsushita, T. Arakaki, N. Kamamoto, M. Sudo, and K. Fujimoto, Sympo. Traffic Flow Self-driven Particles **28**, 5 (2023).

[9] K. Matsushita, T. Arakaki, M. Sudo, N. Kamamoto, and K. Fujimoto, in *Ann. Meeting of JPS* (2023) pp. 22pPSM–28.

[10] K. Matsushita, S. Yabunaka, and K. Fujimoto, J. Phys. Soc. Jpn. **90**, 054801 (2021).

[11] F. Graner and J. A. Glazier, Phys. Rev. Lett. **69**, 2013 (1992).

[12] A. J. Kabla, J. R. Soc. Interface **9**, 3268 (2012).

[13] K. Matsushita, Phys. Rev. E **95**, 032415 (2017).

[14] T. Vicsek, A. Czirók, E. Ben-Jacob, I. Cohen, and O. Shochet, Phys. Rev. Lett. **75**, 1226 (1995).

[15] K. Matsushita, K. Horibe, N. Kamamoto, and K. Fujimoto, J. Phys. Soc. Jpn. **88**, 103801 (2019).

[16] K. Matsushita, Phys. Rev. E **101**, 052410 (2020).

[17] K. Matsushita, H. Hashimura, H. Kuwayama, and K. Fujimoto, J. Phys. Soc. Jpn **91**, 054802 (2022).