新生神経細胞の病的凝縮に対する移動能向上の効果

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概要

成人脳においても、深部領域では新たなニューロンが誕生する。しかしこれらの新生ニューロンは脳損傷部位へ移動できず、損傷修復に寄与できない。最近、松本らはニューロン移動障害がニューロン凝集に起因することを発見した [1]。さらに、分子的な接着強化により凝集が生じると実証した。この凝集を解決することが脳損傷の修復に寄与する可能性がある。本論文では、簡便な解決策として、ニューロン遊走能を促進する治療法を検証した。我々の結果は、遊走促進治療の可能性を示唆する. さらに松本らが提案した接着強化の直接的解決策との併用が効果的である。

Effects of Motility Enhancement on Pathological Aggregation of New Neuron

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Abstract

New neurons are born in a deep region, even in the adult brain. The new neurons cannot migrate into the brain-injured region and, therefore, they cannot repair the injury. Recently, Matsumoto *et al.* found that the migration dysfunction of neurons originates from neuron aggregation [1]. Furthermore, they demonstrated that pathological adhesion of neurons occurs due to the strengthening of molecular adhesion. Solving this aggregation may contribute to the repair of brain injury. In the present paper, as a simple solution, we examine the treatment that enhances neuron motility. Our results imply that the treatment is possible. Furthermore, it suggests that the treatment, combined with a direct solution of adhesion strengthening discussed by Matumoto *et al.*, is effective.

1 Introduction

New neurons possess a remarkable ability to migrate for the development of a highly sophisticated brain structure. Even in the case of the postnatal human brain, new neurons are born, and therefore have the potential to repair brain injury [2]. In this case, because new neurons are born in a deeper region of the brain, the ability to migrate to the brain-injured region is indispensable to supply new neurons to that region. Surprisingly, the new neurons are actually known to have high spontaneous motility and long-distance migration ability [3]. Therefore, the application of their motility to supply new neurons has been well investigated in recent years [4, 5].

Previous investigations have reported that the new neurons exhibit migration disorders into the injured regions. Recently, Matsumoto *et al.* found that the aggregation of new neurons near the injured region leads to migration disorder [1]. Furthermore, they reported that an adhesion molecule, PSA-NCAM [6], is dysfunctional due to its strengthened adhesion [7], which was already known to be the origin of migration disorders [8]. The corresponding model simulation supports the notion that the dysfunction originates from strengthened adhesion. In fact, the reduction of the strengthened adhesion by medical treatment promotes the invasion of new neurons into the injured region.

As a simple solution for aggregating neurons, we can expect a treatment that enhances neuron motility. In recent years, various treatment techniques have made significant progress in guiding new neurons to the injured region [9, 10]. Although the guiding techniques do not simply correspond to an enhancement of motility for our purpose, further progress of related techniques for neuron migration will enable us to enhance neuron motility effectively. To explore the potential application of the treatment, we examine its effect on the aggregation state based on the model.

2 Model

The model is based on the two-dimensional $M+2$-state cellular Potts model on the square lattice [11]. The system simulates the collective migration of $M = 48$ neurons flow through a pipe consisting of glial cells in the brain. The pipe consists of $L_x = 192 \times L_y = 36$ sites in x and y-directions, respectively. Periodic boundary conditions are imposed for these directions, and random obstacles around as follows the previous work [12], $y = 0$ are placed to inhibit the passage through of neurons, as shown in Fig. 1(a) and 1(b).

The configuration of neurons in this model corresponds to domains of Potts states. 0th and $M+1$ domains indicate the extracellular matrix and obstacles consisting of glial cells. Except for the two states, the state corresponding to the cell occupied at the site $\boldsymbol{r}$ is denoted by $m(\boldsymbol{r})$. The mth cell has motility vector $\boldsymbol{p}_m$ and the base position $\boldsymbol{R}_m$. These are initially random.

The configuration changes in a stochastic copy trials. The process is given as the Monte Carlo simulation with the transition probability of Hamiltonian $\mathcal{H}(s)$, where s consists of $\{m(\boldsymbol{r})\}$, $\{(\boldsymbol{p}_m, \boldsymbol{R}_m)\}$. The copy trial is made to a randomly chosen site $\boldsymbol{r}$ from its randomly chosen neighboring site $\boldsymbol{r}'$. The copy is accepted by the Metropolis probability with Boltzmann weight $P(s) = \exp[-\beta\mathcal{H}(s)]$ with $\beta = 0.5$. In a single Monte Carlo step (mcs), $16L_xL_y$ copy trials take place and then p_m is updated by [13–15]

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

Here, $\hat{P}_{\boldsymbol{p}_n}$ is the projection operator to $\boldsymbol{p}_m$, τ is the relaxation time scale of 4.0 and a is the lattice constant. Simultaneously, $\boldsymbol{R}_m$ is updated to the mass center of the mth cell.

Following the previous work [1], we employ the Hamiltonian $\mathcal{H}$ consisting of interface tension $\mathcal{H}_{\rm st}$, volume constriction and elongation $\mathcal{H}_{\rm v}$, motility $\mathcal{H}_{\rm m}$, adhesion $\mathcal{H}_{\rm cca}$, and obstacle $\mathcal{H}_{\rm w}$ parts. The limitation of pages does not permit all the details of these terms and parameters to simulate the saltatory migration of real neurons [16] and the interaction with glial cells [17, 18]. Furthermore, the details are essentially negligible for explaining the aggregation phenomena. Therefore, we only explain the two important terms for our examination on the enhancement of motility here, the motility $\mathcal{H}_{\rm m}$ and the adhesion $\mathcal{H}_{\rm cca}$.

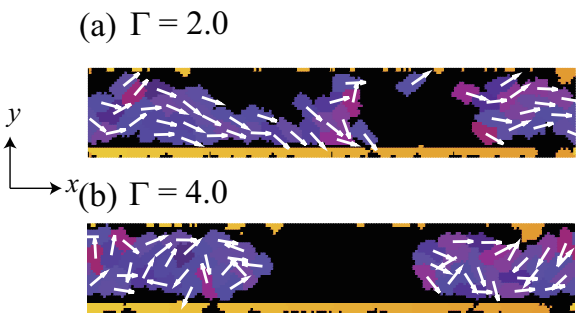

Fig. 1: Typical neuron configuration for (a) $\Gamma = 2.0$ and (b) $\Gamma = 4.0$. The neurons, obstacles, and extracellular matrix are colored purple (or violet), yellow, and black, respectively. Arrows represent the direction of $\boldsymbol{p}_m$.

The motility term [19] is

$$\mathcal{H}_{\rm m} = -\gamma \sum_{\boldsymbol{r}\boldsymbol{r}'} (\zeta_{m(\boldsymbol{r})} + \zeta_{m(\boldsymbol{r}')})\eta_{m(\boldsymbol{r})m(\boldsymbol{r}')}. \tag{2}$$

Here, $\zeta_{m(\boldsymbol{r})}$ is the inner product between the unit vector from $\boldsymbol{R}_{m(\boldsymbol{r})}$ to $\boldsymbol{r}$ and $\boldsymbol{p}_m$. This function indicates that the adhesion molecule density is in the peripheral region of the neuron. η_{kl} is 0 for $k = l$ and otherwise 1. This is introduced to express that the motility arises from mechanical contacts between neurons. This term represents the motility induced by recognition of other neurons. In the present paper, we vary γ to examine the effect of motility enhancement.

This motility reflects mutual recognition of the neurons through their mechanical contacts because of $\eta_{m(\boldsymbol{r})m(\boldsymbol{r}')}$. Therefore, the migrating neurons form a chain structure,in which neurons follow one another through mechanical contacts [20]. This migration mechanism suggests that migration and adhesion are closely linked because adhesion controls the mechanical contacts. Neuron aggregation due to strengthened adhesion may result in migration disorders. Conversely, the motility that induces neuron migration may solve the aggregation effect on the collective migration. This work aims to confirm the existence of such an effect.

The adhesion term [15, 21] is

$$\mathcal{H}_{\rm cca} = -\Gamma \sum_{\boldsymbol{r}\boldsymbol{r}'} \xi_{m(\boldsymbol{r})}\xi_{m(\boldsymbol{r}')}\eta_{m(\boldsymbol{r})m(\boldsymbol{r}')}. \tag{3}$$

Here, $\xi_m = 1 + \lambda\zeta_m$ and we set $\lambda = 0.3$, following the previous work. This adhesion setting represents that adhesion mainly occurs on the cell body side of a neuron. By using these settings, we simulate neuron migration and examine the effect of motility enhancement on aggregation.

3 Result

At first, we confirm the realization of collective migration and aggregation. We obtain a steady state with $\gamma = 1.2$ through the 5×10^3 mcs. Figures 1(a) and 1(b) show the neuron configuration and their migration directions for $\Gamma = 2.0$ and for $\Gamma = 4.0$, respectively. For $\Gamma = 2.0$, the neurons form a chain in the x-direction, and the motility directions exhibit ordering in the same directions. This configuration implies the existence of collective chain migration of neurons. As empirically observed, the new neurons form a cellular chain during their migration. Hence, this result agrees with the empirical knowledge [20].

In contrast, for $\Gamma = 4.0$, the neurons exhibit a relatively compact configuration. Additionally, the motility directions exhibit disorder. These observation suggests that the neurons form an aggregation and are pinned there. The aggregation is also consistent with the empirical observation in the case of strengthened adhesion [1]. From these results, we use the values of Γ to examine driving migration in cases of collective migration and aggregation.

To examine the driving effect on these states, we consider the evaluation of the order parameter and collective velocity in the steady state. Then, we evaluate the time average of the order parameter in the steady state [22]

$$P = \int_T dt \frac{1}{MT} \left| \sum_m \boldsymbol{p}_m(t) \right|. \tag{4}$$

and collective velocity

$$v = \int_T dt \frac{1}{MT} \left| \sum_m \boldsymbol{d}_m(t) \right|. \tag{5}$$

Here, $\boldsymbol{d}_m$ is the displacement of the mth cell per mcs, and $T = 5 \times 10^3$ Monte Carlo steps. If the driving migration solve the neuron aggregation, we can expect that P and v increase with the motility γ. Therefore, we can evaluate the effect through the calculation of these values as a function of γ [1, 14].

Before the discussion of those values, we show a configuration example to get understanding for the enhancement effect of motility for aggregation state. Figure 2(a) shows a snapshot configuration for $\Gamma = 4.0$ and $\gamma = 1.6$. The value of Γ corresponds to the aggregation for $\gamma = 1.2$. In contrast, the neurons exhibit an ordering state of $\boldsymbol{p}_m$ for $\gamma = 1.6$. Therefore, at least, there exists the case that the enhancement of motility solve aggregation state and thereby successfully induces the collective chain migration.

Figure 2(b) shows P as a function of γ. We gives the data for the cases of aggregation $\Gamma = 4.0$, collective migration $\Gamma = 2.0$, individual migration $\Gamma = 0.0$. For low γ, independently of values of Γ, the motility directions take disorder in time average. With increasing γ, the order of motility occurs at

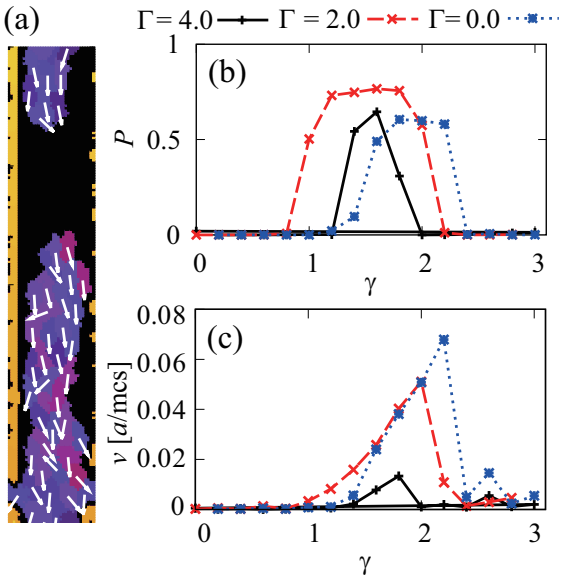

Fig. 2: (a) the configuration for $\Gamma = 4.0$ and $\gamma = 1.6$. The colors and arrows are common with Fig. 1(a) and (b). (b) The order parameter of the motility direction P as a function of the motility γ and (c) the collective velocity v as a function of the motility. The values are calculated for the case of aggregation at $\Gamma = 4.0$ (solid line), that of the collective migration at $\Gamma = 2.0$ (dashed line), and individual migration at $\Gamma = 0.0$ (dotted line)

the lowest value of γ for the case of collective migration, and at a next lower value occurs for the case of aggregation. The motility directions in the case of individuals are mostly difficult to take order for low γ. This result is easily expected to come from its random walk without intercellular adhesion.

With further increasing γ, these cases commonly and abruptly lost their order. The result is consistent with that of a previous work [14]. The motility enhancement is effective for an optimal value as a function of the adhesion. In the case of individual neurons, the order of the motility is maintained at relatively high values of γ [23].

The increasing P in the case of aggregation implies that the increase in γ, namely, the motility enhancement, is at least effective for the occurrence of the motility direction ordering. Therefore, the collective migration may occur in the range of γ. To confirm this, we also show v as a function of γ in Fig. 2(c). The corresponding v for the case of aggregation at $\Gamma = 4.0$ actually increases in the common range of γ for P. However, the values of v are relatively smaller than those of collective migration and individual cases.

In contrast to the case of the aggregation for $\Gamma = 4.0$, the $\Gamma = 2.0$ and $\Gamma = 0.0$ shows relatively high acceleration with increasing γ. In particular,

in the case of $\Gamma = 2.0$, the collective migration occurs in a wide range of γ, including low γ around 1. Therefore, the proper strength of adhesion $\Gamma = 2.0$ for collective migration is most effectively responsive to the motility enhancement in our calculation range.

4 Discussions and Remarks

The present work investigates the enhancement effect of neuron motility on neuron migration. In particular, we focus on mitigating the effects of neuron aggregation resulting from strengthened adhesion. The motility enhancement actually promotes motility ordering in the case of aggregation, despite the strengthened adhesion. The effect on the collective velocity appears to be due to ordering. The effect is relatively small in both collective and individual migration cases.

From this result, the solution for neuron aggregation is a combined use of motility enhancement and normalization of strengthened adhesion. In fact, our results suggest that the motility enhancement mostly promotes the case of the collective migration for $\Gamma = 2.0$. The previous work already provides a technique for normalizing adhesion [1], which can be combined for use in the future.

We also observed in Fig. 2(b) that the abrupt drop of P with increasing γ is common for all cases in our calculation. Therefore, the motility enhancement is limited to a specific range of motility γ. As previously mentioned, this type of collective deceleration commonly occurs in collective migration simulations. The origin of this deceleration is the synergetic effect between the adhesion and the motility, as discussed by Kabla [14]. In the discussion, the high motility breaks the adhesion contacts between neurons, leading to disordered motility directions. In contrast, too low motility cannot promote motion ordering between the neurons. As a result, the proper range of motility for effectively driving collective migration corresponds to cases with comparable values of adhesion and motility.

This explanation, based on the synergetic effect, is only applicable to cases of adhesive contact neurons. However, the abrupt deceleration is also observed in the individual neurons with $\Gamma = 0.0$ for larger γ. In the larger values of γ than 2.4, the low values of v may imply that the neuron shape may be unstable due to high motility in our simulation limit [24]. The small, fluctuating values of v above $\gamma = 2.4$ may reflect instability.

We thank S. Yabunaka and M. Sawada for providing various related knowledge. This work was supported by JSPS KAKENHI (Grant Number 23K03342) and AMED (Grant Number JP19gm1210007).

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