Self-Organized Criticality and Dynamical Crossover in a Stochastic Model of Cell Fate Decision

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We study the asymptotic behaviors of stochastic cell fate decision between proliferation and differentiation. We propose a model of a self-replicating Langevin system, where cells choose their fate (i.e. proliferation or differentiation) depending on local cell density. Based on this model, we propose a scenario for multi-cellular organisms to maintain the density of cells (i.e., homeostasis) through cell-cell interactions, which is regarded as self-organized criticality. Furthermore, we numerically show that the distribution of the number of descendant cells changes over time, thus unifying the previously proposed two models regarding homeostasis: the critical birth death process and the voter model. Our results provide a general platform for the study of stochastic cell fate decision in terms of nonequilibrium statistical mechanics.

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Introduction.— A variety of biological phenomena have been extensively investigated in light of modern nonequilibrium physics. For example, in multicellular organisms, cells actively undergo proliferation (i.e., production of a new cell) and differentiation (i.e., removal from the basal layer; see Fig. 1(a)). Throughout adult life, biological tissues are kept constant in size; they do not expand or shrink drastically. This sort of stationarity, supported by subsequent proliferation and differentiation, is called homeostasis. Since intercellular interactions in cell division kinetics are considered to be crucial during homeostasis, nonequilibrium statistical mechanics of many-body systems is expected to play an important role to clarify the mechanism.

Recent advances in experiments have enabled the tracing of cell fate dynamics (i.e., kinetics of proliferation and differentiation) in adult mammalian tissues. In these experiments, cells in the tissue are labeled by fluorescent proteins, which are inherited to their progeny. Starting from a single labeled cell, the population of the labeled cells (i.e., clone) was observed to expand or shrink stochastically in time (Fig. 1(a)), showing scaling behaviors in the statistics. Most significantly, the average size of surviving clones showed power-law growth $n_{\text{surv}}(t) \sim t^{\delta}$, and the cumulative clone size distribution showed the scaling law $C_n(t) \sim \Phi(n/n_{\text{surv}}(t))$, which both depended on the spatial dimension of the tissue. Theoretically, two nonequilibrium statistical models, the voter model (VM) and the critical birth death process (CBD), have successfully explained distinct experimental situations.

However, there were two problems to be resolved in the previous studies. First, the previous models start from the assumption that the proliferation and differentiation are exactly balanced, meaning that the fine-tuning of parameters is required. Since the population of cells would either exponentially grow or shrink and get extinct if the rates slightly deviated from the balanced parameters, it is critical to address how this fine-tuning is achieved. Second, the microscopic mechanism in which two models (VM and CBD) are realized in biological tissues is not clear. Since both models might not be precisely adopted in real tissues, a natural question that arises is what happens in the intermediate regime between these models.

In this letter, we propose a novel model of cell fate decision with intercellular interactions, which overcome the aforementioned issues. In our model, the population of cells is regarded as a self-replicating many-body Langevin system, where we incorporate intercellular interaction in the self-replication process through local cell density. We find that homeostasis is maintained in this model without the fine-tuning of parameters, meaning that global cell density is autonomously kept constant on average. Furthermore, we show that the previously proposed VM and CBD scenarios are incorporated in our model as the small and large limits of the cell-cell interaction range. This indicates that the interaction range of the density-dependent replication process is a key in determining which model of the two appears in biological tissues. We find that in the case of the intermediate value of the interaction range, the clone size statistics cross over from the CBD statistics to the VM statistics as time evolves. We propose that by evaluating the timing of the crossover in experiment, we can indirectly infer the interaction range of the fate decision dynamics in the tissue. Our results also reveal a natural scenario in which VM can arise in real experimental setups.

Model.— We model the population of cells as an interacting many-particle system with $\{x_k(t)\}_{k=1}^{N(t)}$ being the position of the center of the $N(t)$ cells existing on the basal layer at time $t$ (see Fig. 2(a)). Although our model can be extended to higher dimensions, we here...
focus on the one-dimensional case in order to study the distinct limits of asymptotic behavior. Neighboring cells in a tissue are typically attached to each other by cell-cell adhesion. We incorporate this interaction by the following many-body Langevin equations \[ \frac{d}{dt}x_j(t) = -\frac{\partial}{\partial x_j}U(\{x_k\}) + \xi_j(t). \] (1)

Here, \( \xi_j(t) \)'s represent the white Gaussian noise satisfying \( \langle \xi_j(t) \rangle = 0, \quad \langle \xi_j(t) \xi_k(s) \rangle = 2D\delta_{j,k}\delta(t-s) \) (2) for \( j, k = 1, \ldots, N(t) \). Initial positions of the cells are prepared so that the label of the cells are ordered as \( x_{k-1} \leq x_k \leq x_{k+1} \), and the periodic boundary condition is employed. A positive constant \( D \) is the noise strength and \( U(\{x_k\}) = \sum_k u(|x_k - x_{k+1}|) \) denotes the two-body interaction, which describes the cell-cell adhesion between nearest neighbors. For simplicity, we set \( u(X) = K(X - l_0)^2/2 \). The strength of the adhesive potential \( K \) determines a typical time scale for spatial relaxation, and the natural length \( l_0 \) determines a typical length scale of a cell.

Before describing the replication process in our model, we briefly review the previous studies of cell fate decision. As mentioned above, two stochastic models were introduced to explain the clone size statistics in experiments: \( \delta = 1/2 \) and \( \Phi(X) = e^{-\pi X^2/4} \) in one-dimension [4], and \( \delta = 1 \) and \( \Phi(X) = e^{-X} \) in two-dimension [5]. VM explains the experimental results both in one-dimension [4, 6] and in two-dimension [6, 15], where cell proliferation directly triggers the differentiation of a neighboring cell to compensate for the loss (Fig. 1(b)). However, the clone size statistics in two-dimension, are also explained by CBD (Fig. 1(c)) [5, 6], where the decision between proliferation and differentiation is made independently, with equal probabilities. In both of the two models, the fine-tuning of the parameters is assumed to maintain the homeostasis.

A crucial point of our model is that the tissue homeostasis is achieved as a consequence of the cell-cell interaction, rather than the finely tuned birth/death probabilities. To this end, we assume that the local cell density affects the cell fate decision process [10, 11]. We define the local cell density \( \rho_L(x) \) as:

\[ \rho_L(x) := \frac{1}{2L} \int_{x-L}^{x+L} dy \sum_j \delta(y - x_j), \] (3)

where \( L \) denotes the interaction range of cell-cell interactions. The interaction range \( L \) corresponds to the biologically relevant length scale of the cell fate regulation through local cell density. A proliferating cell (PC) at position \( x \) undergoes the following birth-death process with rates \( w^\pm \) that depend on local cell density (see Fig. 2(a)):

\[ PC \xrightarrow{\lambda_1} \begin{cases} PC + PC & \text{with rate } w^+(\rho_L(x)) \\ \emptyset & \text{with rate } w^-(\rho_L(x)) \end{cases}, \] (4)

where \( \emptyset \) denotes differentiation (i.e., removal from the basal layer), and the typical timescale is set by \( \lambda_1^{-1} \). Note that although a multi-type branching process has been introduced in previous studies [5, 12], we here focus...
on the single-type birth-death process \(1\) to analyze the asymptotic clone size statistics.

We assume that \(F(\rho) := w^+ (\rho) - w^- (\rho)\) has an attractive fixed point \(\rho = \rho^*\) such that \(F(\rho^*) = 0\) and \(F'(\rho^*) < 0\), where \(F'(\rho) := dF(\rho)/d\rho\). An important role of the attractive fixed point \(\rho = \rho^*\) is to regulate cell fate through local cell density in an autonomous fashion (see Fig. 2(b)). This is analogous to self-organized criticality, where power-law behaviors emerge within the attractor of a spatially extended dynamical system, even without fine-tuning of external parameters (e.g., temperature \(17\), \(18\)). We will see in our model that the power law and scaling law in the clone size statistics appear at the fixed point of cell density, corresponding to the situation where homeostasis is achieved.

Equations \(1\) are discretized and numerically solved by the Euler-Maruyama method. The cell fate decision process \(4\) is implemented as follows. When a cell undergoes proliferation, the local cell density \(\rho_t\) is evaluated for newly born cells, and two lifetimes \(\tau^\pm\) are generated from exponential distributions with rates \(\lambda w^\pm(\rho_t)\), respectively. If \(\tau^+ < \tau^-\), the cell undergoes proliferation after time \(\tau^+\), and otherwise it undergoes differentiation after time \(\tau^-\). In order to study the asymptotic clone size statistics, we introduce the label degree of freedom to cells, where only one single cell is initially labeled, mimicking the marker protein in experiments. The quantities of interest are the average clone size of the labeled progeny \(l(t) := \int_0^t \rho_s(\tau) d\tau\) and the labeled clone size distribution \(C_n(t)\) which is defined as the probability that a clone with at least \(n\) labelled cells.

We remark on the stability of the model. When \(L\) is sufficiently large, the population of cells tends to form spatial clustering. This is regarded as an example of the Brownian bug problem, which has been observed in various models with self-replication and diffusion \(19\). We performed linear stability analysis of our model \(13\), and identified the linearly stable region as shown in Fig. 2(c), where the clustering of cells does not occur.

**Main results.**—We now discuss our numerical results. Figure 3(a) shows the time evolution of the average clone size for several values of \(L\). The average clone size grows linearly in the short time scale, and exhibits the power-law growth with exponent 1/2 in the long time scale. Figure 3(b) shows that the clone size distribution is the exponential form in the short time, and then crosses over to the half-Gaussian form in the long time scale. These results imply that the clone size statistics cross over from the CBD statistics with \(\delta = 1\) and \(\Phi(X) = e^{-X}\) to the VM statistics with \(\delta = 1/2\) and \(\Phi(X) = e^{-\pi X^2/4}\) in the course of time.

In order to clarify the dynamical crossover of the clone size statistics, we consider the two opposite limits of the interaction range \(L\). Since the interaction range \(L\) lies between the cell size \(l_0\) and the system size (i.e., the size of the tissue) \(L_{\text{Sys}}\), we call the two limits \(L \to l_0\) and \(L \to L_{\text{Sys}}\) the small \(L\) limit and the large \(L\) limit, respectively. Figures 3(c) and 3(d) show the time evolution of the clone size distributions for the large and the small \(L\) limit, respectively. The inset in Fig. 3(c) or 3(d) shows the time evolution of the average clone size. The clone size statistics asymptotically approach to the CBD statistics in the large \(L\) limit and to the VM statistics in the small \(L\) limit. These results imply that the CBD statistics and the VM statistics are formulated in a unified view through the interaction range \(L\).

In the following, we consider the mechanism that gives rise to the CBD statistics and the VM statistics in the large and small \(L\) limit, where the existence of the attractive fixed point \(\rho = \rho^*\) plays a significant role. In the large \(L\) limit, the cell fate regulation is governed by global cell density \(\rho(t)\) in the continuum limit as \(L_{\text{Sys}} \to \infty\):

\[\lambda^{-1} \frac{d}{dt} \rho = (w^+ (\rho) - w^- (\rho)) \rho = F(\rho) \rho.\]  

The existence of an attractive fixed point \(\rho^*\) of \(F(\rho)\) ensures homeostasis so that \(w^+ (\rho^*) = w^- (\rho^*)\) holds in the long time scale, leading to self-organized criticality \(17\). Therefore, the clone size statistics are expected to behave asymptotically as the CBD statistics: \(\delta = 1\) and \(\Phi(X) = e^{-X}\). We emphasize that in our model, the critical clone size statistics are achieved as a result of cell-cell interactions through cell density, in contrast to CBD.
where the criticality is assumed by the fine-tuning of the birth/death probabilities. In other words, the asymptotic CBD statistics can be understood as the consequence of cell fate regulation by the long-range interaction through cell density.

On the other hand, in the case of small $L$, the cell-cell interaction is effectively short-ranged, because the ever-expanding average size of the surviving clones $l(t)$ is always larger than $L$. In this case, as soon as a proliferating cell undergoes differentiation, the proliferation rate increases locally around that position, and the neighboring cells will be likely to compensate for the loss of the adjacent cell. Therefore, the resulting clone size statistics are expected to asymptotically behave as the VM statistics with $\delta = 1/2$ and $\Phi(X) = e^{-X^2/4}$. In other words, our model implies that the VM statistics can naturally arise as a result of short-range interaction through cell density.

We now focus on the case of $l_0 \ll L \ll L_{\text{Sys}}$, to consider the dynamical crossover of the clone size statistics. The dynamical crossover takes place due to the competition between two length scales: the interaction range $L$ and the ever-expanding average clone size $l(t)$. In the short time scale with $l(t) \ll L$, the cell fate regulation is effectively governed by global cell density, leading to the CBD statistics. On the other hand, in the long time scale with $l(t) \gg L$, the cell fate regulation is effectively governed by local cell density, leading to the VM statistics. This implies the dynamical crossover of the clone size statistics in one-dimension.

**Scaling hypothesis.**— Our numerical results suggest that the time scale for the crossover increases with the interaction range $L$. The dynamical crossover takes place due to the competition between the interaction range $L$ and the average clone size $l(t)$. Since the average clone size is ever-increasing in time, one expects that $l(t)$ exceeds $L$ at certain time $t_c$. We refer to $t_c$ as the crossover time, at which the behavior of the clone size statistics change. Since the clone size statistics are effectively the CBD statistics in short time scale, the crossover time $t_c$ is estimated from the following equation:

$$L = l(t_c) \simeq l_{\text{CBD}}(t_c) = l_0 \left(1 + \frac{1}{2} \lambda t_c\right), \quad (6)$$

where the average clone size $l(t)$ is approximated by the exact expression of that of the CBD statistics: $l_{\text{CBD}}(t) = l_0(1 + \lambda t/2)$. Therefore, we expect that $t_c(L) = 2\lambda^{-1}(L - l_0)/l_0$. Scaling the time by the crossover time $t_c(L)$, and scaling the average clone size $l(t)$ by the interaction range $L$, all curves collapse onto a single master curve, as shown in Fig. 4. From Fig. 4, we find that the average clone size $l(t)$ has the following scaling form:

$$\frac{l(t) - l_0}{L} = f\left(\frac{t}{t_c(L)}\right) \begin{cases} \simeq \frac{t}{t_c(L)} & t \ll t_c(L), \\ \sim \left(\frac{t}{t_c(L)}\right)^{1/2} & t \gg t_c(L), \end{cases} \quad (7)$$

which reconfirms the CBD statistics and the one-dimensional VM statistics.

From the scaling form of $l(t)$, we find that the interaction range $L$ in a tissue can be estimated from $L = l_0(1 + \lambda t_c/2)$, where $t_c$ is obtained by fitting experimental data to the $l(t)$ curve. Although there is no evidence of dynamical crossover in the current data, future experiments at finer spatio-temporal scale at the earliest stage of clone size expansion may be capable of elucidating the key length scale of cell-cell interactions in the mechanism of tissue homeostasis.

**Concluding remarks.**— We presented a novel model of stochastic cell fate decision, based on cell-cell interactions through local cell density. In our model, previous two stochastic models (i.e., CBD and VM) are unified by introducing the interaction range $L$. We numerically studied the asymptotic clone size statistics for the one-dimensional case. The asymptotic clone size statistics of CBD and VM are realized in the large and small limits of $L$, respectively. In the case of intermediate $L$, the clone size statistics cross over from that of CBD to that of VM in the course of time. Furthermore, we studied the scaling hypothesis for the dynamical crossover of the average clone size.

Although the mechanism of tissue homeostasis has not yet been revealed at the level of molecular biology, our phenomenological analysis has quantitatively elucidated the role of the time and length scales of cell-cell interactions. We note that the clone size statistics in the one-dimensional tissue experiments is the only demonstration.
of VM in real experiments, and our study has revealed a natural scenario of the VM statistics to emerge in biological systems.

We expect that our analysis would provide a platform for further studies. For instance, the scenario of cell fate decision in two-dimensional tissues is still unsettled, since CBD and VM have the same asymptotic statistics, apart from the logarithmic correction in the average clone size [6]. On the basis of our model, it is left for future studies to discuss the spatial correlation of labeled cell configuration to clarify the cell fate decision scenario in sheet tissues.

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SUPPLEMENTAL MATERIAL

DYNAMICAL CROSSOVER IN A STOCHASTIC MODEL OF CELL FATE DECISION

In this Supplemental Material, we discuss the stability of the spatially uniform distribution of cells in our model. In our numerical simulation, we have observed that the population of cells exhibits spatial clustering, when the interaction range $L$ is sufficiently large. Similar phenomena have been reported in a variety of systems, which has been known as the Brownian bug problem [S1, S2, S3, S4]. In the following, we give a simple scenario of the spatial clustering, and clarify the parameter region in which the spatial clustering does not occur and the uniform distribution is linearly stable.

Microscopic Equation of Motion

We briefly review the setup to discuss the linear stability. Although our analysis in the main text is limited only in one-dimensional case, we now deal with our model for a general dimension $d$. We consider a population of proliferating cells, which are confined within the $d$-dimensional progenitor cell pool, let $\{\bar{x}_k(t)\}_{k=1}^{N(t)}$ be the set of coordinates of the centers of them. Here $N(t)$ denotes the number of cells at time $t$. We assume that the cells obey the following overdamped Langevin equations:

$$ \frac{d}{dt} \bar{x}_j(t) = -\nabla_j U (\{\bar{x}_k(t)\}) + \xi_j(t), $$

(S1)

for $j = 1, 2, \ldots, N(t)$, where $\nabla_j = \partial / \partial \bar{x}_j$, and $\xi_j(t)$’s denote independent white Gaussian noise terms satisfying $\langle \xi_j(t) \rangle = 0, \langle \xi_j(t) \xi_k(s) \rangle = 2D \delta_{jk} \delta(t-s)$ for $j, k = 1, \ldots, N$ and $\mu, \nu = 1, \ldots, d$, with the noise intensity $D > 0$. $U (\{\bar{x}_k(t)\})$ denotes the interaction potential among neighboring cells. In particular, we assume the following form: $U (\{\bar{x}_k(t)\}) = \sum_j \sum_{k \neq j} u(\bar{x}_j - \bar{x}_k)$, which represents stored force acting among neighboring cells, mimicking the cell adhesion forces. The two-body potential is assumed to include only short-range interaction; for example we can take following form:

$$ u(\bar{x}) = |\bar{x}|^2, $$

(S2)

where a new cell is created at the position $\bar{x}$ as a birth event occurs, while the cell simply annihilates as a death event occurs. The birth and death rates $w^+ (\rho_L(\bar{x}))$ depend on the local density of cells $\rho_L(\bar{x}; t)$, which is defined as:

$$ \rho_L(\bar{x}; t) := \frac{1}{|D_L(\bar{x})|} \int_{D_L(\bar{x})} d\bar{y} \sum_{k=1}^{N(t)} \delta(\bar{y} - \bar{x}_k(t)) $$

(S3)

with $D_L(\bar{x}) = \{ \bar{y} \in \mathbb{R}^d \mid |\bar{y} - \bar{x}| < L \}$. The parameter $L$, which we call the interaction range, expresses the length scale within which a cell can respond to change in the local density.

Continuum Description

We discuss the linear stability around the spatially uniform distribution of cells [S6]. To this end, we consider the coarse-grained or continuum description of the many-body Langevin equations [S1]. In the continuum description, the population of the cell is described by the coarse-grained local density field $\rho(\bar{x}; t)$ in $\mathbb{R}^d$. By following the argument by Dean [S2], we obtain the dynamical equation for the local density field:

$$ \frac{\partial}{\partial t} \rho(\bar{x}; t) = D \nabla^2 \rho(\bar{x}; t) + \nabla \cdot \left( \rho(\bar{x}; t) \nabla \Psi(\bar{x}; t) \right) $$

$$ + \nabla \cdot \left( \sqrt{2D \rho(\bar{x}; t)} \eta(\bar{x}; t) \right) + \lambda F(\rho_L(\bar{x}; t)) \rho_L(\bar{x}; t) + \sqrt{2DG(\rho_L(\bar{x}; t))} \zeta(\bar{x}; t), $$

(S4)

where $\eta(\bar{x}; t)$ and $\zeta(\bar{x}; t)$ are white Gaussian noise fields satisfying

$$ \langle \eta^\mu(\bar{x}; t) \rangle = 0, \quad \langle \eta^\mu(\bar{x}; t) \eta^{\nu}(\bar{y}; s) \rangle = \delta_{\mu, \nu} \delta(t-s) \delta^d(\bar{x} - \bar{y}) $$

$$ \langle \zeta(\bar{x}; t) \rangle = 0, \quad \langle \zeta(\bar{x}; t) \zeta(\bar{y}; s) \rangle = \delta(t-s) \delta^d(\bar{x} - \bar{y}) $$

(S5)

with Itô’s forward discretization ($\mu, \nu = 1, 2, \ldots, d$). $\Psi(\bar{x}; t)$ in the first line and $F(\rho)$ and $G(\rho)$ in the second line are given by

$$ \Psi(\bar{x}; t) := \int d^d \bar{y} \rho(\bar{y}; t) u(\bar{x} - \bar{y}), $$

(S6)

$$ F(\rho) := (w^+(\rho) - w^-(\rho)), $$

(S7)

$$ G(\rho) := \sqrt{(w^+(\rho) + w^-(\rho)) \rho}. $$

(S8)

Linearization

We next focus on the local density field averaged over the noise. Let $\langle \rho(\bar{x}; t) \rangle$ be the ensemble average of $\rho(\bar{x}; t)$.
By noting that the noise term is given by the Itô product in Eq. (S1), we obtain
\[
\frac{\partial}{\partial t} \langle \rho(\vec{x}; t) \rangle = D \nabla^2 \langle \rho(\vec{x}; t) \rangle + \nabla \cdot \left( \langle \rho(\vec{x}; t) \nabla \Psi(\vec{x}; t) \rangle \right) + \lambda \left( F(\rho_L(\vec{x}; t)) \rho_L(\vec{x}; t) \right)
\]  
(S9)

Equation (S9) has a nontrivial stationary solution \( \langle \rho(\vec{x}; t) \rangle = \rho^* > 0 \), which expresses the stationary and uniform density satisfying \( w^+(\rho^*) = w^- (\rho^*) \). Whether this homogeneous steady state is stable or unstable against small perturbations can be investigated by linearization around \( \langle \rho(\vec{x}; t) \rangle = \rho^* \). We insert \( \langle \rho(\vec{x}; t) \rangle = \rho^* + \delta \rho(\vec{x}; t) \) to Eq. (S9), then expand each term around \( \langle \rho(\vec{x}; t) \rangle = \rho^* \), and pick up only linear terms. The second and third terms in Eq. (S9) are linearized as:
\[
\lambda F(\rho_L(\vec{x}; t)) \rho_L(\vec{x}; t) = \lambda F'(\rho^*) \rho^* \delta \rho_L(\vec{x}; t) + O((\delta \rho)^2)
\]  
(S10)

and
\[
\nabla \cdot \left( \langle \rho(\vec{x}; t) \nabla \Psi(\vec{x}; t) \rangle \right) = \nabla \cdot \left( \langle \rho^* + \delta \rho(\vec{x}; t) \rangle \nabla \Psi(\vec{x}; t) \right)
\]  
(S11)

In the last line, we have used the following approximation
\[
\nabla^2 \Psi(\vec{x}; t)
\]  
(S12)

We have assumed that \( \delta \rho(\vec{y}; t) \) varies slowly enough on the support of \( u(\vec{x} - \vec{y}) \), so that the integral yields \( \delta \rho(\vec{x}; t) \) with a coefficient \( \gamma = \int d^d \delta \rho(\vec{y}; t) u(\vec{x} - \vec{y}) \). The parameters in Eq. (S14) turn out to be
\[
\alpha = -\lambda F'(\rho^*) \rho^*, \quad \beta = D + \rho^* \gamma K.
\]  
(S13)

Therefore, Eq. (S9) is linearized as:
\[
\frac{\partial}{\partial t} \delta \rho(\vec{x}; t) = -\alpha \delta \rho_L(\vec{x}; t) + \beta \nabla^2 \delta \rho(\vec{x}; t),
\]  
(S14)

where positive parameters \( \alpha, \beta \) are set by
\[
\alpha := -\lambda F'(\rho^*) \rho^*, \quad \beta := D + \rho^* \gamma K.
\]  
(S15)

**Linear Stability**

We are now in the position to perform the linear stability analysis. First we decompose Eq. (S14) into the Fourier mode with wavenumber \( \vec{k} \). The Fourier decomposition of the first term in the right hand side of Eq. (S14) takes the form:
\[
\int d^d \vec{x} e^{-i \vec{k} \cdot \vec{x}} \delta \rho_L(\vec{x}; t)
\]  
(S16)

Here, \( \mathcal{I}_d(kL) \) is defined as
\[
\mathcal{I}_d(kL) := \frac{1}{|D_L(\vec{0})|} \int_{D_L(\vec{0})} d^d \vec{k} e^{i \vec{k} \cdot \vec{r}}
\]  
(S17)

with \( D_L(\vec{0}) = \{ \vec{R} \in \mathbb{R}^d \mid |\vec{R}| < L \} \). Then we obtain
\[
\frac{\partial}{\partial t} \delta \rho(\vec{k}; t) = -\alpha \mathcal{I}_d(kL) \delta \rho(\vec{k}; t) - \beta k^2 \delta \rho(\vec{k}; t). \]  
(S18)

For \( d = 1 \), we have
\[
\mathcal{I}_1(kL) = \frac{1}{2L} \int_{-L}^{L} dxe^{ikx} = \frac{\sin(kL)}{2kL} = \frac{\sin(kL)}{kL},
\]  
(S19)

and for \( d = 2 \),
\[
\mathcal{I}_2(kL) = \frac{1}{\pi L^2} \int_0^L rdr \int_0^{2\pi} d\theta e^{ikr \cos \theta}
\]  
(S20)

where \( J_n(\xi) \) is the Bessel function.

Small perturbation with Fourier mode \( \vec{k} \) grows as \( \delta \rho(\vec{k}; t) \propto e^{\nu(k)t} \) with the growth rate:
\[
\nu(k) := -\alpha \mathcal{I}_d(kL) - \beta k^2.
\]  
(S21)

If \( \nu(k) > 0 \), any small perturbation grows exponentially, and therefore the spatially uniform distribution is linearly unstable. On the other hand, if \( \nu(k) < 0 \), it is linearly stable.
Linear stability for \( d = 1 \)

For \( d = 1 \), the growth rate

\[
\nu(k) = -\alpha \frac{\sin(kL)}{kL} - \beta k^2 \tag{S22}
\]

has nontrivial zeros in the range \( k \in (0, +\infty) \) if and only if

\[
\frac{3\beta}{\alpha L^2} X_1^2 + \cos(X_1) \leq 0, \tag{S23}
\]

with \( X_1 \equiv \min \left\{ \xi \in (0, +\infty) \mid \tan \xi = \frac{1}{3} \xi \right\} \approx 4.08. \)

Therefore, it turns out that the spatially homogeneous distribution \( \rho(\vec{x}; t) = \rho^* \) is linearly unstable if and only if

\[
\frac{\beta}{\alpha L^2} \leq \frac{\cos(X_1)}{3X_1^2} \approx 0.012, \tag{S24}
\]

which implies that the spatially homogeneous distribution becomes unstable with sufficiently large \( L \) and small \( \frac{\beta}{\alpha} \). Note that the ratio \( \frac{\beta}{\alpha} \) is proportional to \( K/\lambda \) when \( T \) is sufficiently small. Therefore, roughly speaking, spatially homogeneous distribution requires \( K/\lambda L^2 \gg 1 \).

Linear stability for \( d = 2 \)

For \( d = 2 \), the growth rate

\[
\nu(k) = -\alpha \frac{2J_1(kL)}{kL} - \beta k^2 \tag{S25}
\]

has nontrivial zeros in the range \( k \in (0, +\infty) \) if and only if

\[
\frac{6\beta}{\alpha L^2} X_2^2 + (J_0(X_2) - J_2(X_2)) \leq 0, \tag{S26}
\]

with \( X_2 \equiv \min \left\{ \xi \in (0, +\infty) \mid \frac{J_1(\xi)}{J_0(\xi) - J_2(\xi)} = \frac{1}{6} \xi \right\} \approx 4.78. \) The condition for the linear instability is given by

\[
\frac{\beta}{\alpha L^2} \leq -\frac{J_0(X_2) - J_2(X_2)}{6X_2^2} \approx 0.0027. \tag{S27}
\]

The conditions obtained for \( d = 1 \) and \( d = 2 \) are shown in Fig S1. When the dimensionless ratio \( \frac{\beta}{\alpha L^2} \) exceeds a certain threshold, the growth rate \( \nu(k) \) no longer has any nontrivial zero. The growth rate for \( d = 1 \) is shown in Fig S2. Unstable modes with \( \nu(k) > 0 \) appear in the case of sufficiently small values of \( \frac{\beta}{\alpha L^2} \). The phase diagram for \( d = 1 \) obtained by the linear stability analysis is shown in the main text, where the green curve separates the linearly unstable phase (the upper region) and the linearly stable phase (lower region).

![Fig. S1. Condition of the existence of nontrivial zeros of \( \beta/\alpha L \) for \( d = 1 \) (left panel) and \( d = 2 \) (right panel). Parametric curves (represented by red, magenta, and green) given by function \( \sin(kL) \) have at least one common point with the reference curve \( \cos(X) \) in (0, +\infty) if and only if \( \beta/\alpha L \approx 1 \) and \( \beta/\alpha L \approx 0 \). The conditions \( \beta/\alpha L \leq 1 \) for \( d = 1 \) and \( \beta/\alpha L \leq 2 \) for \( d = 2 \) are shown respectively.](image)

![Fig. S2. The growth rates \( \nu(k) \) for \( d = 1 \) are plotted for some parameters (left panel). The right panel is reproduced at the enlarged scale from the left panel. Those modes with \( \nu(k) > 0 \) are referred to unstable modes.](image)

### Discussion

The appearance of the spatial clustering can be interpreted in terms of the competition between the timescale of the division kinetics and that of the cell adhesion. The intuitive interpretation is as follows. Within the scope of the linear stability analysis, the cell adhesion contributes to the time evolution of the local density field via the diffusion term with a diffusion constant \( K \). The timescale for a cell, which exits from the center of the spherical region to the outside of the spherical region, is proportional to \( L^2/K \). Suppose that this timescale \( L^2/K \) is much larger than the typical timescale of division \( \lambda^{-1} \), i.e., \( K/\lambda L^2 \ll 1 \). In this case, before a cell produced by the cell division travels the length scale of \( L \), cells will be produced by cell divisions one after another. Since the total population of cells is kept almost constant, it leads to the spatial clustering of cells. The condition for the equilibration of the two timescales \( K/\lambda L^2 = 1 \) separates the spatially clustering phase from the spatially homogeneous phase. In the latter phase, our model is expected to behave as a suitable model of a biological
tissue at steady state. Note that the discussion above is irrespective of the spatial dimension \(d\).

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