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Supplementary Material: Interplay between the persistent random walk and the contact inhibition of locomotion leads to collective cell behaviors

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Supplementary Text

To help understand how our model works, we provide an example of the formulation of a simple system consisting of two cells (I = 1-2) interacting with five focal adhesion (FA) points (i = 1-5) into the matrix equation **Ku** = **f** (Fig. S3). It is assumed that two front cell-points are adjacent to each other so that they experience drag forces.

Multiplication of the first four rows of **K** to **u** corresponds to Eq. 1 for four cell-points. The last three elements in **u** are the magnitude of contractile forces exerted on each cell-point by FA points. Since we assume that the magnitudes of all contractile forces acting on one cell-point are identical, they can be represented by one quantity (i.e. $F_I = \left|\mathbf{F}_{\mathrm{c},i}\right|$ for all $i \in R_I$). Cell-points that do not interact with any FA point (e.g. the rear cell-point of the second cell with I = 2) are excluded from this part of **u** because their contractile forces will be zero. The block 1 of **K** looks like a square diagonal matrix with the angular drag coefficient (γ). The block 3 has the sum of the vector Δ_{Ii} for each cell-point interacting with FA points. Because we assume that the direction of contractile force ($\mathbf{F}_{\mathrm{c},i}$) is always perpendicular to that of Δ_{Ii}, multiplication of elements in the block 3 to the magnitude of contractile forces results in the sum of torques exerted on each cell-point by the forces.

Multiplication of the rows 5-12 of **K** to **u** corresponds to Eq. 2. The elements 5-12 in **u** are x and y components of velocities of cell-points, and the elements 5-12 in **f** are x and y components of a spring force acting between front and rear cell-points described by Eq. 3. The block 5 of **K** looks like a sparse square matrix with three drag coefficients: α, β, and η. Elements in the block 6 are the sum of unit vectors indicating the directions of $\mathbf{F}_{\mathrm{c},i}$. Multiplication of these

elements to the magnitude of contractile forces results in the sum of force vectors $\mathbf{F}_{c,i}$ acting on each cell-point.

Multiplication of the last three rows of **K** to **u** corresponds to the kinematic constraint represented by Eq. 4. Note that cell-points without interacting FA points do not need this kinematic constraint. For each cell-point, one of the FA points is randomly selected. Then, Δ_{Ii} and $\mathbf{L}_{Ii}$ of the selected FA point are used for the blocks 7 and 8. For example, the index "*i*" in the row 13 (for the front cell-point of the first cell with $I = 1$) can be either 2 or 3. Admittedly, depending on the random selection, the directions of instantaneous velocities of cell-points can change. However, FA points in one active adhesion region of a front cell-point are located adjacently to each other, so the directions of velocities will not be very different. Also, since different FA points are randomly selected at each time point, the net displacement of the cell-point after some time will be directed toward those FA points in average. Multiplication of elements in the block 7 to angular velocities in **u** results in the magnitudes of tangential velocities of the cell-points with an assumption that the tangential points do not move at the time moments. Multiplication of elements in the block 8 to x and y components of the velocities of cell-points in **u** results in the magnitudes of the velocities. The kinematic constraint means that these two magnitudes are the same.

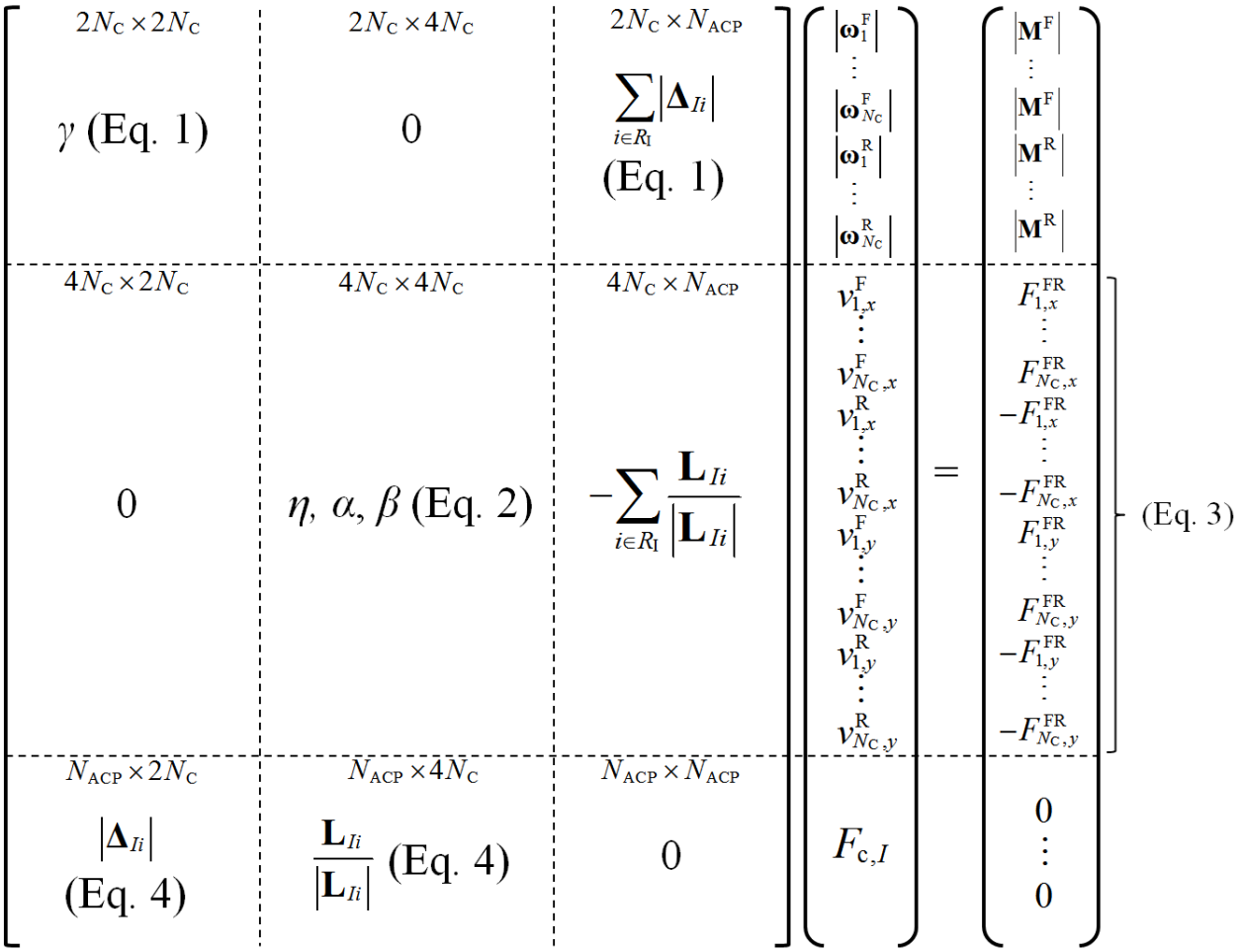


Figure S1 Constitution of the matrix equation. This figure shows elements in the matrix equation, **Ku** = **f** (Eq. 5). Equation numbers are written, wherever possible, to indicate where elements originate from. Summations (Σ) for two blocks in the matrix **K** are performed for all focal adhesion points interacting with each cell-point. The vector **u** has the magnitude of $\boldsymbol{\omega}_I$ and the x and y components of $\mathbf{v}_I^F$ and $\mathbf{v}_I^R$ as well as the magnitude of contractile forces exerted on a cell-point, I. The size of each block of the matrix **K** is shown on the top of the block, where N_C and N_S are the total number of cells and substrate points, respectively, and N_{ACP} is the number of cell-points interacting with focal adhesion points. Subscripts F and R indicate front and rear cell-points, respectively. Definitions of the vectors $\boldsymbol{\Delta}_{Ii}$ and $\mathbf{L}_{Ii}$ are shown in Fig. 1c

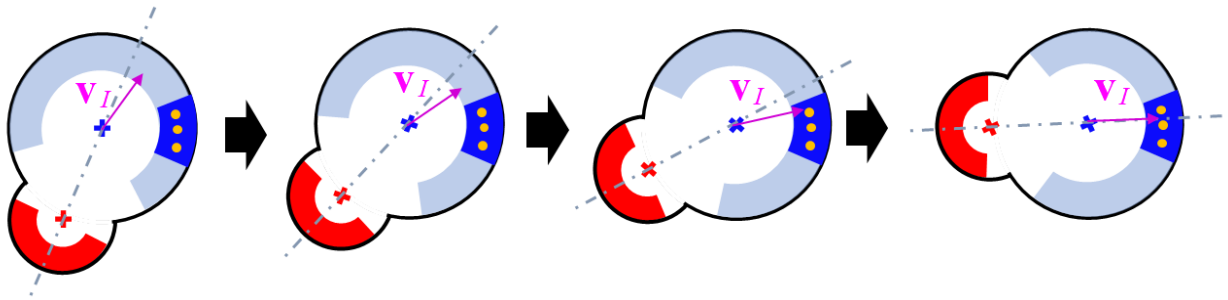
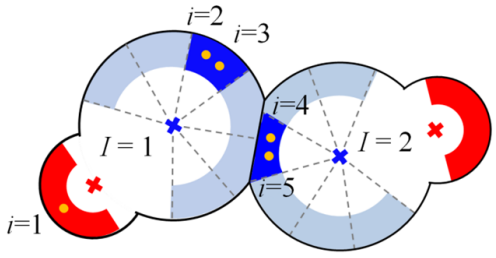


Figure S2 Formation of lamellipodia and the reorientation of a cell. After a section in the front adhesion region is activated as lamellipodium, the angular range of the new section defined with respect to space is memorized. Even if the cell orientation is changed, the same angular range is used for determining whether or not a substrate point is assigned to this section as a focal adhesion point till the section is deactivated. A cell in the schematic diagram gradually rotates clockwise due to contractile forces exerted consistently in the same direction by focal adhesion points. The direction of the instantaneous velocity of the front cell-point ($\mathbf{v}_l$) is not always parallel to the cell orientation because a change in the cell orientation takes more time

a



b

$$
\begin{bmatrix}
\boxed{1} & \boxed{2} & \boxed{3} \\
\begin{matrix}\gamma & 0 & 0 & 0\\ 0 & \gamma & 0 & 0\\ 0 & 0 & \gamma & 0\\ 0 & 0 & 0 & \gamma\end{matrix} & 0 & \begin{matrix}|\Delta^{\mathrm{F}}_{1,2}|+|\Delta^{\mathrm{F}}_{1,3}| & 0 & 0\\ 0 & |\Delta^{\mathrm{F}}_{2,4}|+|\Delta^{\mathrm{F}}_{2,5}| & 0\\ 0 & 0 & |\Delta^{\mathrm{R}}_{1,1}|\\ 0 & 0 & 0\end{matrix} \\
\boxed{4} & \boxed{5} & \boxed{6} \\
0 & \begin{matrix}\eta+\alpha+\beta & -\beta & -\alpha & 0 & 0 & 0 & 0 & 0\\ -\beta & \eta+\alpha+\beta & 0 & -\alpha & 0 & 0 & 0 & 0\\ -\alpha & 0 & \eta+\alpha & 0 & 0 & 0 & 0 & 0\\ 0 & -\alpha & 0 & \eta+\alpha & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & \eta+\alpha+\beta & -\beta & -\alpha & 0\\ 0 & 0 & 0 & 0 & -\beta & \eta+\alpha+\beta & 0 & -\alpha\\ 0 & 0 & 0 & 0 & -\alpha & 0 & \eta+\alpha & 0\\ 0 & 0 & 0 & 0 & 0 & -\alpha & 0 & \eta+\alpha\end{matrix} & \begin{matrix}-\frac{L^{\mathrm{F}}_{1,2,x}}{|\mathbf{L}^{\mathrm{F}}_{1,2}|}-\frac{L^{\mathrm{F}}_{1,3,x}}{|\mathbf{L}^{\mathrm{F}}_{1,3}|} & 0 & 0\\ 0 & -\frac{L^{\mathrm{F}}_{2,4,x}}{|\mathbf{L}^{\mathrm{F}}_{2,4}|}-\frac{L^{\mathrm{F}}_{2,5,x}}{|\mathbf{L}^{\mathrm{F}}_{2,5}|} & 0\\ 0 & 0 & -\frac{L^{\mathrm{R}}_{1,1,x}}{|\mathbf{L}^{\mathrm{R}}_{1,1}|}\\ 0 & 0 & 0\\ -\frac{L^{\mathrm{F}}_{1,2,y}}{|\mathbf{L}^{\mathrm{F}}_{1,2}|}-\frac{L^{\mathrm{F}}_{1,3,y}}{|\mathbf{L}^{\mathrm{F}}_{1,3}|} & 0 & 0\\ 0 & -\frac{L^{\mathrm{F}}_{2,4,y}}{|\mathbf{L}^{\mathrm{F}}_{2,4}|}-\frac{L^{\mathrm{F}}_{2,5,y}}{|\mathbf{L}^{\mathrm{F}}_{2,5}|} & 0\\ 0 & 0 & -\frac{L^{\mathrm{R}}_{1,1,y}}{|\mathbf{L}^{\mathrm{R}}_{1,1}|}\\ 0 & 0 & 0\end{matrix} \\
\boxed{7} & \boxed{8} & \boxed{9} \\
\begin{matrix}|\Delta^{\mathrm{F}}_{1,i}| & 0 & 0 & 0\\ 0 & |\Delta^{\mathrm{F}}_{2,i}| & 0 & 0\\ 0 & 0 & |\Delta^{\mathrm{R}}_{1,i}| & 0\end{matrix} & \begin{matrix}\frac{L^{\mathrm{F}}_{1,i,x}}{|\mathbf{L}^{\mathrm{F}}_{1,i}|} & 0 & 0 & 0 & \frac{L^{\mathrm{F}}_{1,i,y}}{|\mathbf{L}^{\mathrm{F}}_{1,i}|} & 0 & 0 & 0\\ 0 & \frac{L^{\mathrm{F}}_{2,i,x}}{|\mathbf{L}^{\mathrm{F}}_{2,i}|} & 0 & 0 & 0 & \frac{L^{\mathrm{F}}_{2,i,y}}{|\mathbf{L}^{\mathrm{F}}_{2,i}|} & 0 & 0\\ 0 & 0 & \frac{L^{\mathrm{R}}_{1,i,x}}{|\mathbf{L}^{\mathrm{R}}_{1,i}|} & 0 & 0 & 0 & \frac{L^{\mathrm{R}}_{1,i,y}}{|\mathbf{L}^{\mathrm{R}}_{1,i}|} & 0\end{matrix} & 0
\end{bmatrix}
\begin{pmatrix}
|\boldsymbol{\omega}^{\mathrm{F}}_{1}| \\ |\boldsymbol{\omega}^{\mathrm{F}}_{2}| \\ |\boldsymbol{\omega}^{\mathrm{R}}_{1}| \\ |\boldsymbol{\omega}^{\mathrm{R}}_{2}| \\ v^{\mathrm{F}}_{1,x} \\ v^{\mathrm{F}}_{2,x} \\ v^{\mathrm{R}}_{1,x} \\ v^{\mathrm{R}}_{2,x} \\ v^{\mathrm{F}}_{1,y} \\ v^{\mathrm{F}}_{2,y} \\ v^{\mathrm{R}}_{1,y} \\ v^{\mathrm{R}}_{2,y} \\ F^{\mathrm{F}}_{\mathrm{c},1} \\ F^{\mathrm{F}}_{\mathrm{c},2} \\ F^{\mathrm{R}}_{\mathrm{c},1}
\end{pmatrix}
=
\begin{pmatrix}
|\mathbf{M}^{\mathrm{F}}| \\ |\mathbf{M}^{\mathrm{F}}| \\ |\mathbf{M}^{\mathrm{R}}| \\ |\mathbf{M}^{\mathrm{R}}| \\ F^{\mathrm{FR}}_{1,x} \\ F^{\mathrm{FR}}_{2,x} \\ -F^{\mathrm{FR}}_{1,x} \\ -F^{\mathrm{FR}}_{2,x} \\ F^{\mathrm{FR}}_{1,y} \\ F^{\mathrm{FR}}_{2,y} \\ -F^{\mathrm{FR}}_{1,y} \\ -F^{\mathrm{FR}}_{2,y} \\ 0 \\ 0 \\ 0
\end{pmatrix}
$$

Figure S3 Example of the formulation of a simple system. **a** A system consisting of two cells (I = 1, 2) interacting with focal adhesion points (orange dots, i = 1-5). Each cell is composed of front (blue) and rear (red) cell-points. Two front cell-points are adjacent to each other so that they experience drag forces with β. **b** Structure of the matrix equation, **Ku** = **f**. Elements in each block of the matrix and vectors are explained in detail in Supplementary Text

Table 1 Parameter values used in the model

Parameter	Definition	Value
$R_{R,in}$	Inner radius of the rear adhesion region	4 [μm]
$R_{R,out}$	Outer radius of the rear adhesion region	10 [μm]
θ_R	Angular span of the rear adhesion region	180 [deg]
$R_{F,in}$	Inner radius of the front adhesion region	6 [μm]
$R_{F,out}$	Outer radius of the front adhesion region	14 [μm]
θ_F	Total angular span of the front adhesion region	180, 240, 300 [deg]
T_F	Duration of each section in the front adhesion region	1-60 [min]
N_F	The number of sections in the front adhesion region	6
S	Sensitivity to contact	0-0.75
κ	Spring constant between front and rear cell-points	50 [nN/μm]
r_0^{FR}	Equilibrium distance between front and rear cell-points	8 [μm]
$\mathbf{M}^F$	Torque generated by front cell-points	850 [nN·μm]
$\mathbf{M}^R$	Torque generated by rear cell-points	20 [nN·μm]
d_c	Aerial density of cells	140-1000 [cells/mm^2]
n	Aerial density of substrate points	16 $\times 10^4$ [cells/mm^2]
γ	Angular drag coefficient	20 [nN.μm.hr]
η	Drag coefficient due to a surrounding medium and an underlying substrate	0.2 [nN·hr/μm]
α	Drag coefficient between front and rear cell-points	0.1 [nN·hr/μm]
β	Drag coefficient between neighboring cell-points that belong to different cells	0.1 [nN·hr/μm]
r_{crit}	Critical distance within which cell-points belonging to different cells feel drag forces	8 [μm]

Movie Captions

Movie 1 Migration of multiple cells for 20 hr with dynamic formation of lamellipodia without sensitivity to contact. Cells slow down or stop to avoid contact to other cells, indicative of the contact inhibition of locomotion. In this case, cell density is 780 mm^{-2}, domain size is 0.5 × 0.5 mm, and a periodic boundary condition exists. The front adhesion region with the total angular span of 180° is divided into 6 sections, and only one of them can be activated at once for 6 min

Movie 2 Collective migration of cells at high cell density for 60 hr with dynamic formation of lamellipodia without sensitivity to contact. Cells show more confined motions due to very frequent contact to other cells. In this case, cell density is 2,300 mm^{-2}, domain size is 0.5 × 0.5 mm, and a periodic boundary condition exists. The front adhesion region with the total angular span of 180° is divided into 6 sections, and only one of them can be activated at once and then lasts for 6 min

Movie 3 Ordered behaviors of cells for 60 hr with dynamic formation of lamellipodia and high sensitivity to contact. Nematic ordering emerges from indirect interactions of cells through the underlying substrate without direct repulsive forces between cells. In this case, cell density is 2,300 mm^{-2}, domain size is 0.5 × 0.5 mm, and a periodic boundary condition exists. The front adhesion region with the total angular span of 180° is divided into 6 sections, and only one of them can be activated at once for 6 min. The sensitivity to contact used in this case is 0.75