Report in AS-IOP AAC mini-workshop:

Dynamic self-organization in living organisms and active matter

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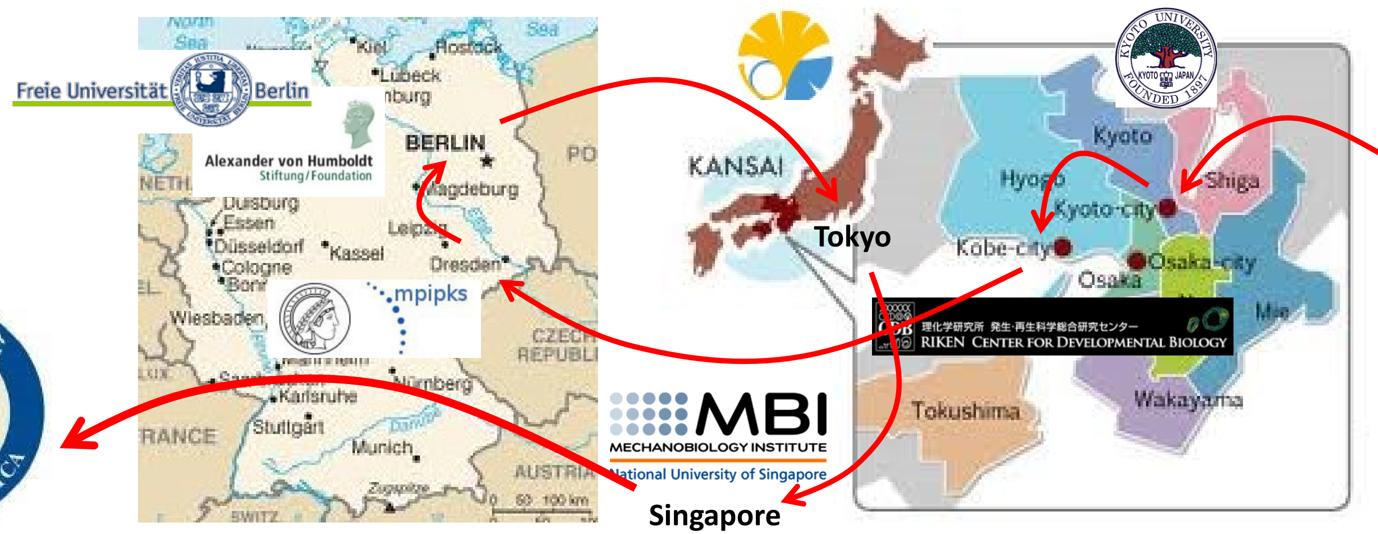
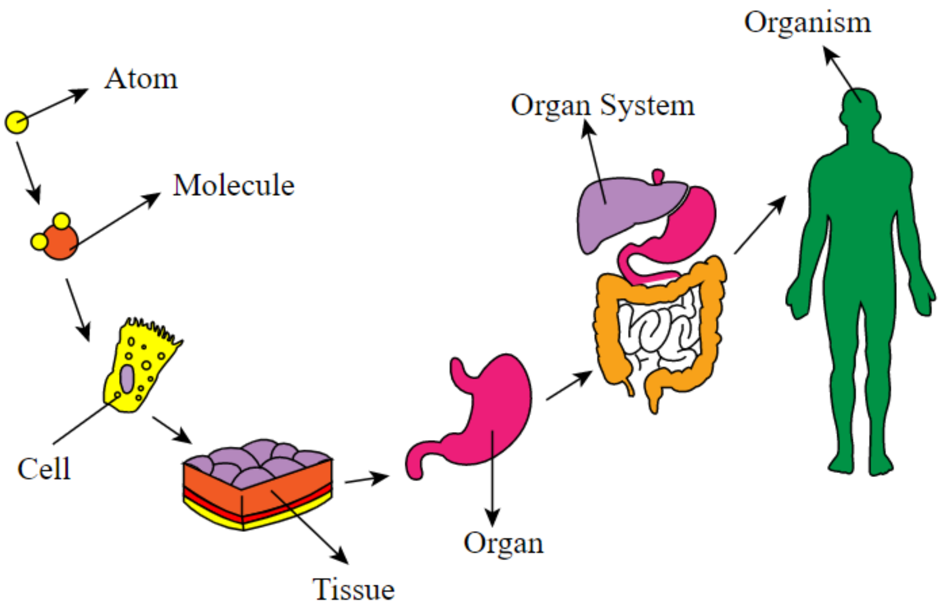
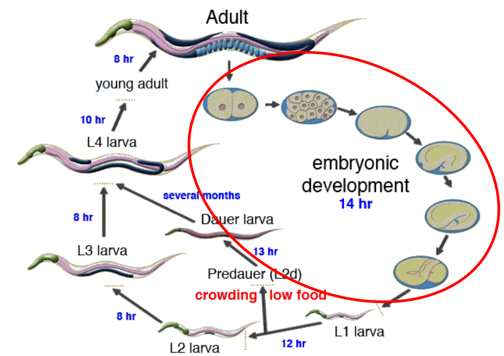
Personal website: https://sites.google.com/site/tetsuyahiraiwa
Group website: https://theorphysbiolgroup.wixsite.com/oursite

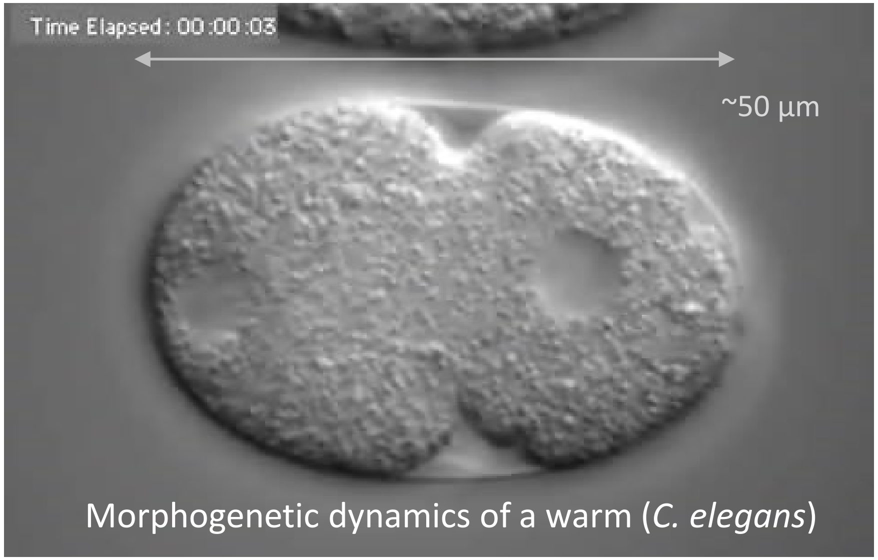


From this April

Living organisms and emergent properties







Morphogenetic dynamics of a warm (*C. elegans*)

- ***Living organisms are full of emergent properties.***
- ***Views of dynamics and self-organizing processes are important.***

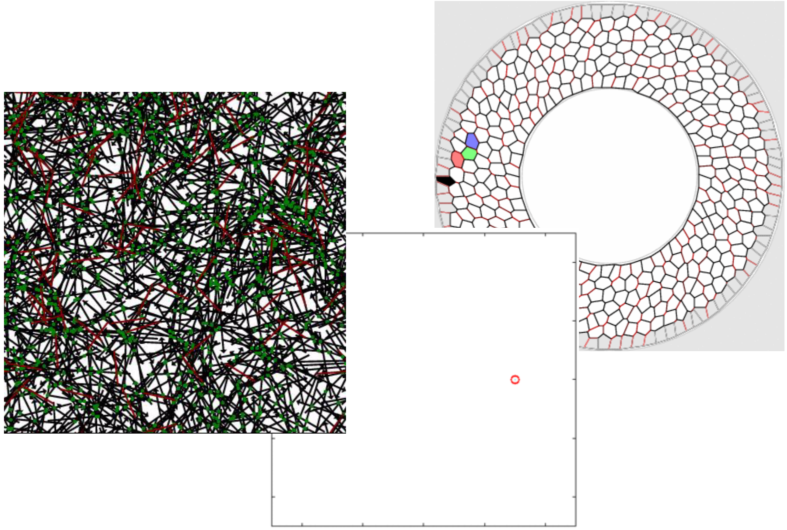
Figure from
https://www.chegg.com/learn/biology/anatomy-physiology-in-biology/levels-of-organization-of-body

Movie from
https://goldsteinlab.weebly.com/
http://labs.bio.unc.edu/Goldstein/movies.html/

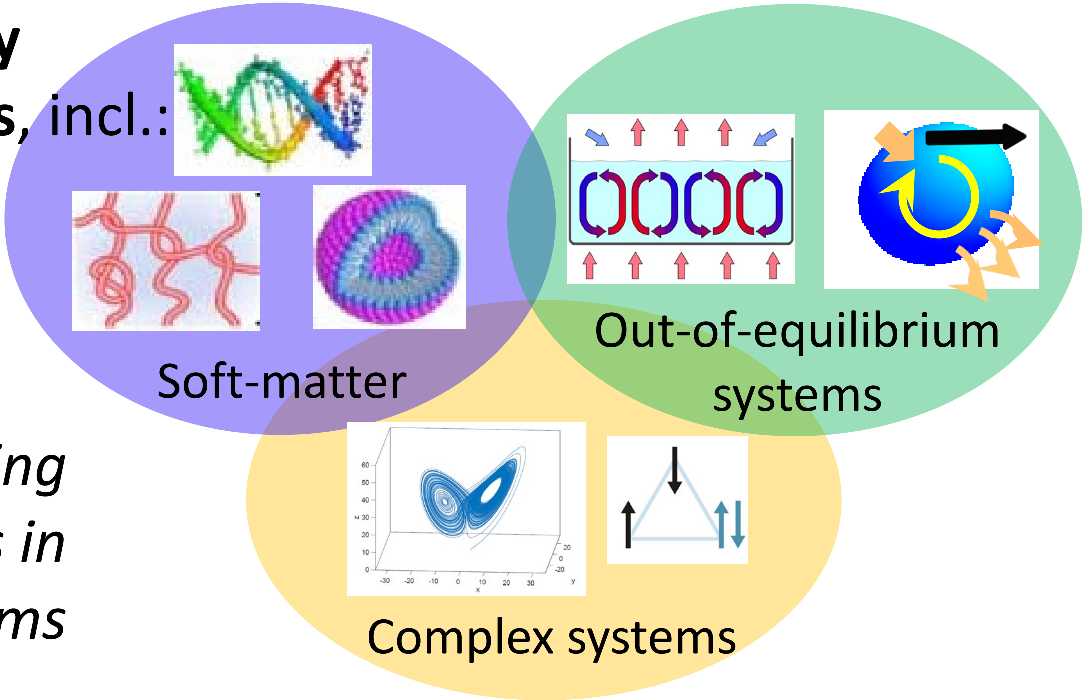
Pictures from
https://www.sfu.ca/biology/faculty/hutter/hutterlab/research/Celegans.html

Our approach

Studying emergent properties in living organisms theoretically…



- from **mechanical point of views**
- based on **concepts to study physics of complex natures,** incl.:



New scheme of understanding emergent processes in living organisms

Top right movies are from: **Hiraiwa**, Salbreux, *PRL.* (2016); **Hiraiwa**, et al., *Phys. Biol.* (2014); #Sato, #**Hiraiwa**, #Maekawa, …, #Kuranaga, *Nat. Commun*. (2015)

Bottom left figures are from: https://universe-review.ca/I15-81-softmatter.jpg; https://www.mechanobio.info/; Wikipedia - Biophysics; Wikipedia - Dissipative_system (in Jpn)

Our works for these 5 years

Collective cell migration

Hiraiwa* (2022) EPJE (Topic. Collect. "Tissue Mechanics")
Hiraiwa* (2020) PRL
Hayakawa, **Hiraiwa**, …, Shibata* (2020) eLife.
Hiraiwa* (2019) PRE

Chromatin organization and dynamics

Das*, …, Prost*, **Hiraiwa*** arXiv
Das*, …, **Hiraiwa*** (2022) eLife

- Names of myself and our lab members at MBI (Dr. Das, Dr. Lou) and IOP are bolded
- # denotes shared first authorship.
- * denotes contact authors

Lab personnel so far

2 Postdocs (Dr. Lou, Dr. Das; appearing as 1st authors above) @Mechanobiology Institute, National University of Singapore (- March 2023)

1 Postdoc, 1 PhD Student @IOP, AS (April 2023 -)

Tissue morphogenesis and homeostasis

Mukenhirn, …, **Hiraiwa**, …, Honigmann* bioRxiv
Lou*, …, Hiraiwa*, Saunders* (2023) PRL
Kawaue, …, **Lou**, …, **Hiraiwa**, …, Toyama* (2023) Dev. Cell.
Lou*, …, **Hiraiwa*** (2022) Biomech. Model. Mechanobiol.
Yamamoto*, **Hiraiwa,** Shibata* (2020) PRResearch
<Review article> **Hiraiwa***, …, Kuranaga* (2019) Symmetry

Active matter physics collaborations

#Hiraiwa*, #Akiyama, ..., Kakugo (2022) Phys. Chem. Chem. Phys.
Afroze, …, **Hiraiwa**, ... Kakugo* (2021) Biochem. Biophys. Res. Commun.
Sakamoto, …, **Hiraiwa**, …, Maeda, Miyazaki* (2020). Nat. Commun.
Tanida*, …, **Hiraiwa*** …, Sano* (2020). PRE

Cell/tissue-simulation method collaborations

Tanida, …, **Hiraiwa***, Nonomura*, Sano*. Will be submitted in a few days.
Okuda*, **Hiraiwa** (2023) EPJE
<Review article> Delanoë-Ayari*, **Hiraiwa***, …, Saw* (2023) Int. J. Biochem. Cell Biol.
Okuda*, **Hiraiwa** (2023) PRE
Okuda*, …, **Hiraiwa** (2022) EPJE
<Review article> #Fuji, #Tanida, …, **#Hiraiwa*** (2022) Sem. Cell Dev. Biol.

The details can be found in my personal Google site (https://sites.google.com/site/tetsuyahiraiwa)

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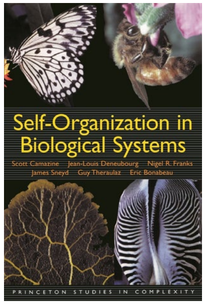
Dynamic Self-Organization (DSO) in living organisms

Self-organization =
"is a process in which pattern at the global level of a system emerges solely from numerous interactions among lower-level component of the system"



Quate from the textbook: Camazine "Self-organization in Biological Systems" Princeton University Press (2003)

Many other books and review articles on self-organization in biology recently : e.g.
Karsenti "Self-organization in cell biology: a brief history" Nat. Rev. Mol. Cell Biol. 9, 255 (2008).
Collinet, Lecuit "Programmed and self-organized flow of information during morphogenesis" Nat. Rev. Mol. Cell Biol. 22, 245 (2021).
etc.

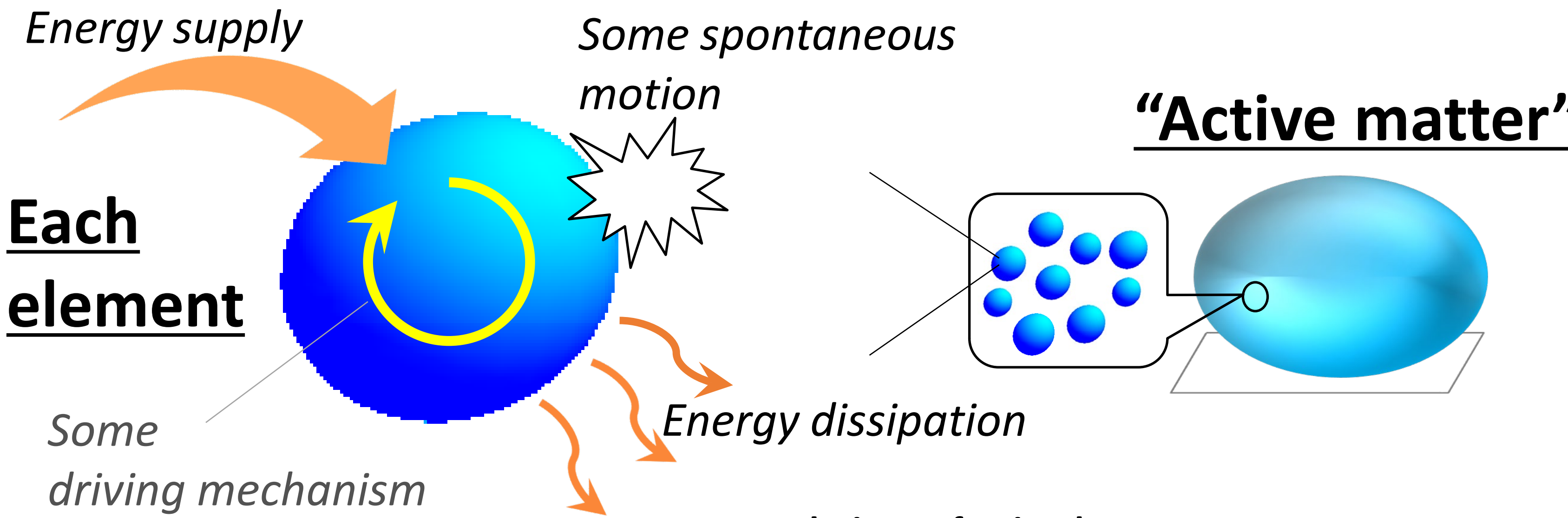
◆ Grand questions around self-organization in living organisms

- **How intracellular multimolecular structures/patterns and their dynamics are formed and maintained?** ***-> Cell biology***
- **How shapes and coherent dynamics of animate multicellular assembly are formed and maintained?** ***-> Developmental biology***
- **What we can learn from living systems to tame artificial self-organizing system?** ***-> Bio-inspired material/system science, Active matter science***

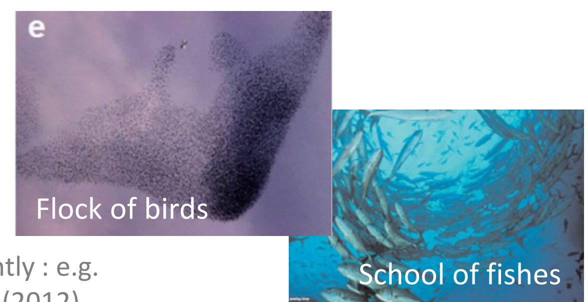
Figure from https://www.chegg.com/learn/biology/anatomy-physiology-in-biology/levels-of-organization-of-body

Dynamic Self-organization (DSO) in/of Active Matter

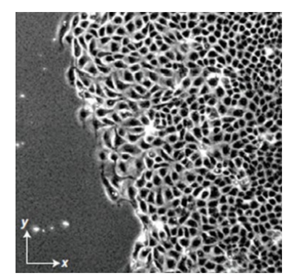
= Material/System consisting of the elements each of which converts supplied energy to its motion



Ex. Populations of animals

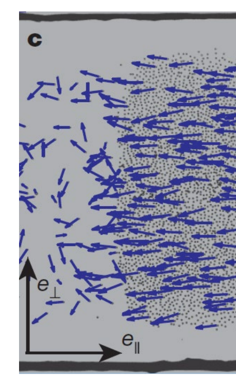


Ex. Assembly of living cells



Photos from: Vicsek et al. 2012 review

Ex. Collective of Colloids



Bricard et al. Nature '13

Many review articles on self-organization in biology recently : e.g.
Vicsek et al. "Collective Motion", Physics Reports 517, 71 (2012).
MacKintosh et al., "Active Cellular Materials" Curr. Op. Cell Biol. 22, 29–35 (2010).
Marchetti et al., "Hydrodynamics of soft active matter" Rev. Mod. Phys. 85, 1143 (2013).
Ramaswamy, "The Mechanics and Statistics of Active Matter" Annu. Rev. C. M. Phys. 1, 323 (2010).
etc...

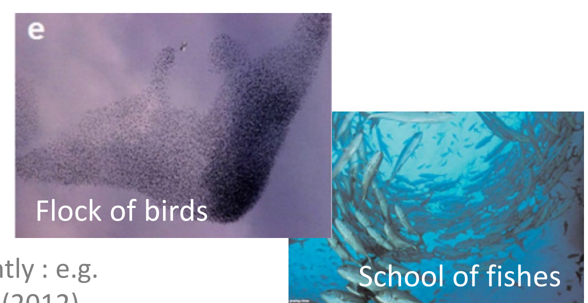
Dynamic Self-organization (DSO) in/of Active Matter

= Material/System consisting of the elements each of which converts supplied energy to its motion

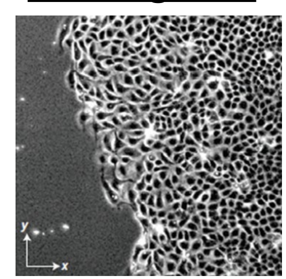
◆ **Grand questions around dynamic self-organization in/of active matter**

- **What generic features it has?** (We haven't been working so far.)
- **How we can control their dynamic self-organization, or coherent motion?**
- **How active matter concept can explain some aspects of complex-material systems such as living systems?**

Ex. Populations of animals



Ex. Assembly of living cells



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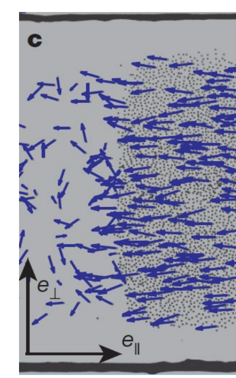

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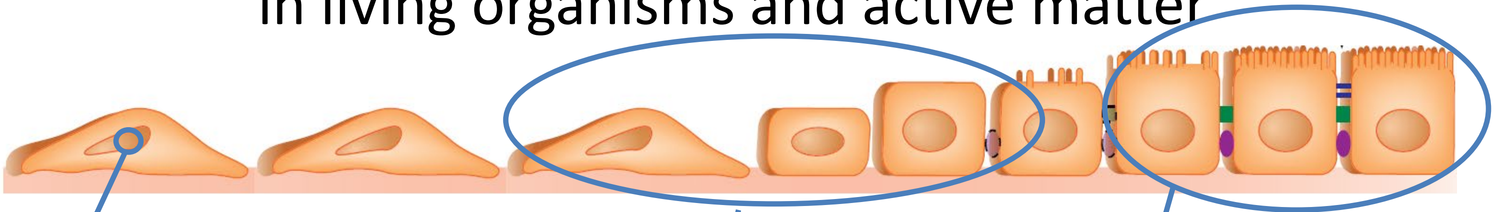
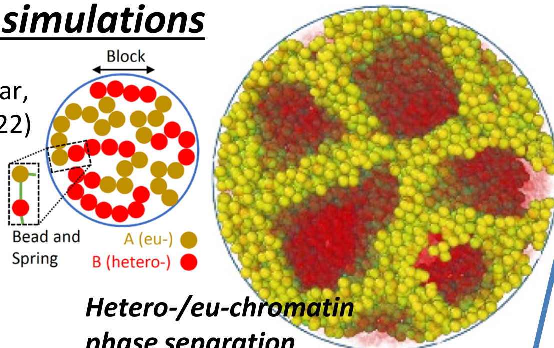
Theoretical studies on (dynamic) self-organization in living organisms and active matter



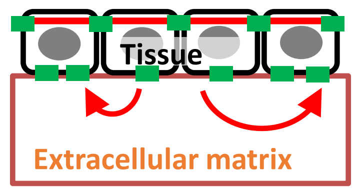
Chromatin organization and dynamics; based on polymer-physics simulations

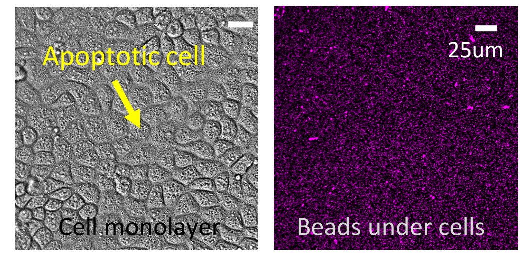
Das, Sakaue, Shivashankar, Prost, **Hiraiwa,** *eLife* (2022)



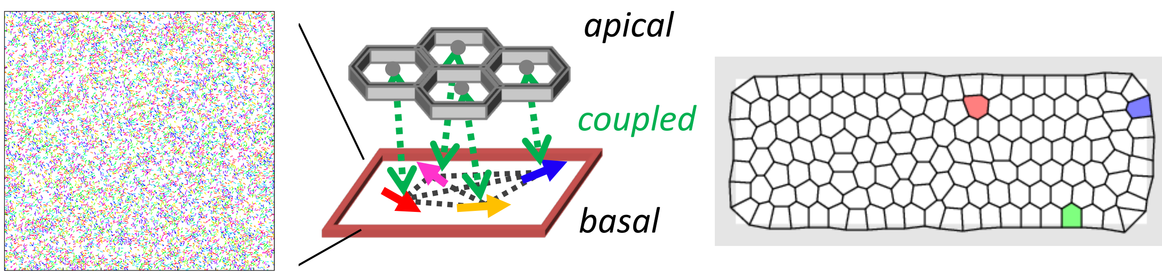
Tissue morphogenesis and homeostasis; with continuum-mechanics theory

Lou, Kawaue, Yow, Toyama, Prost, **Hiraiwa**, *Biomech. Model. Mechanobiol.* (2022).





Collective cell migration; by individual cell-based stochastic dynamics

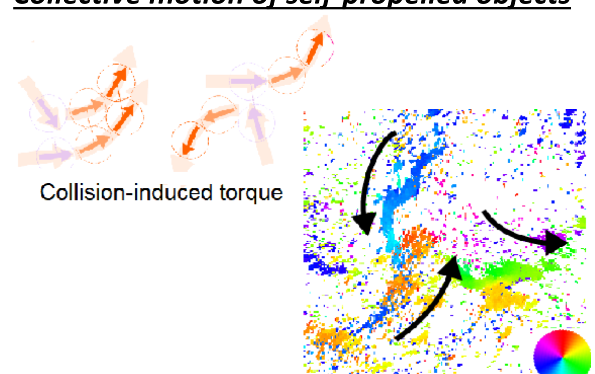


Hiraiwa, *Phys. Rev. Lett.* (2020).

Hiraiwa, *EPJE Topical Issue "Tissue Mechanics"* (2022).

Ex. of collaborations with external groups

Collective motion of self-propelled objects



Hiraiwa, Akiyama et al. *Phys. Chem. Chem. Phys.* (2022).

Lab personnel	2 Postdocs (Dr. Lou, Dr. Das; appearing as first authors above) @Mechanobiology Institute, National University of Singapore (- March 2023) 1 Postdoc, 1 PhD Student @IOP, AS (April 2023 -)

Top figure: Adapted from : https://www.mechanobio.info/development/what-is-the-epithelial-to-mesenchymal-transition-emt/

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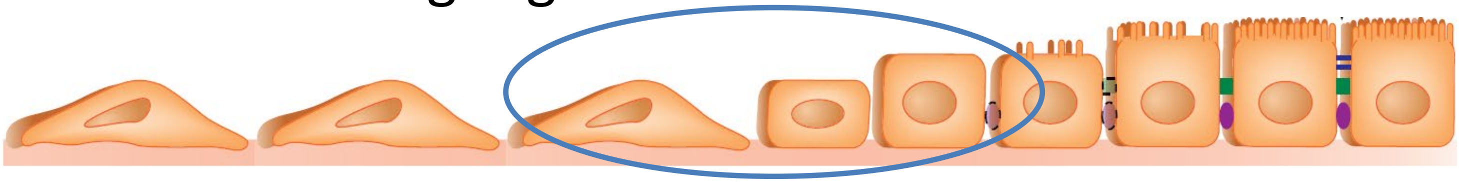

◆ <u>Questions around self-organization in living organisms</u>

- How intracellular multimolecular structures/patterns and their dynamics are formed and maintained? -> Cell Biology

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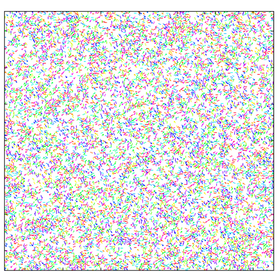
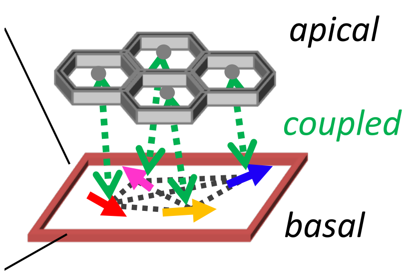
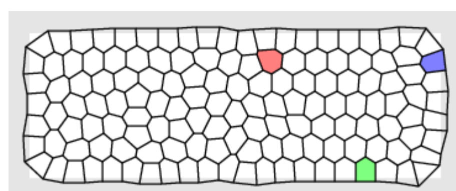






Hiraiwa, *Phys. Rev. Lett.* (2020).

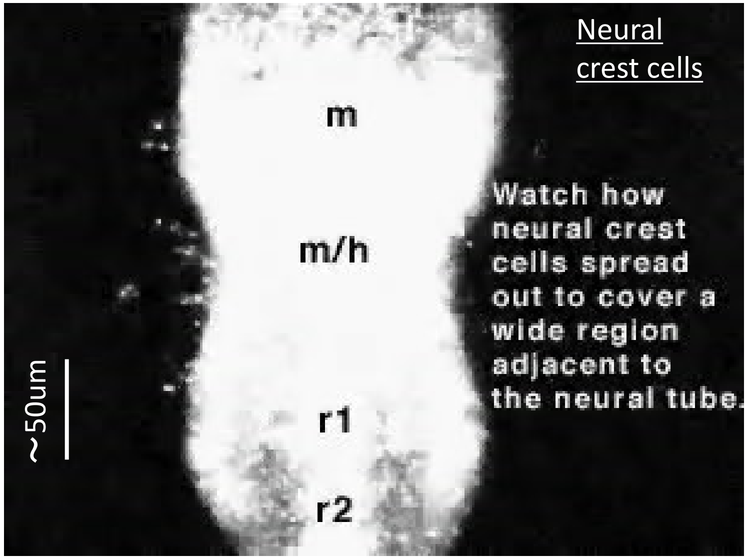
Hiraiwa, *EPJE Topical Issue "Tissue Mechanics"* (2022).

Top figure: Adapted from : https://www.mechanobio.info/development/what-is-the-epithelial-to-mesenchymal-transition-emt/

Motivation

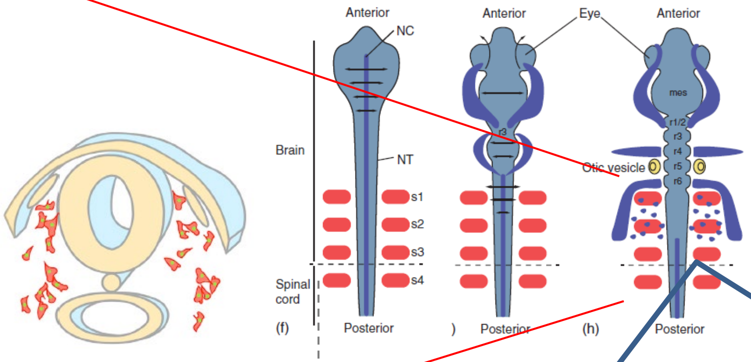
◆ To explore the ability of ***cell-cell communication*** to form various cooperative behaviors and dynamic structures — ***"dynamic self-organization (DSO)"*** — of ***migrating cells***

Example

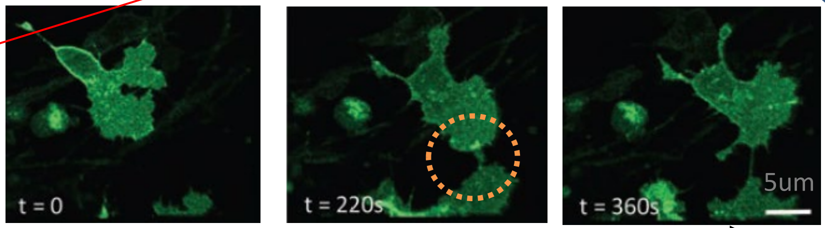


Kulesa et al. Development ('00)

Morphogenetic process (Chick hindbrain)



Theveneau et al. In: eLS. John Wiley & Sons, Ltd: Chichester (2015)



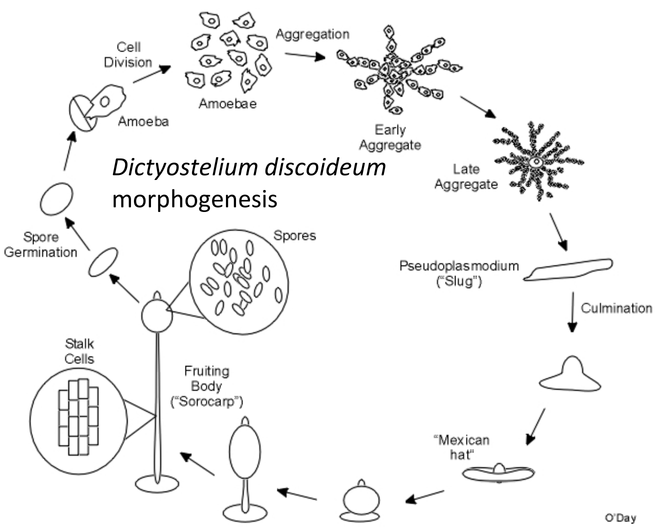
Cell-cell communication

Li et al. Cell Rep. 26, 1489 '19

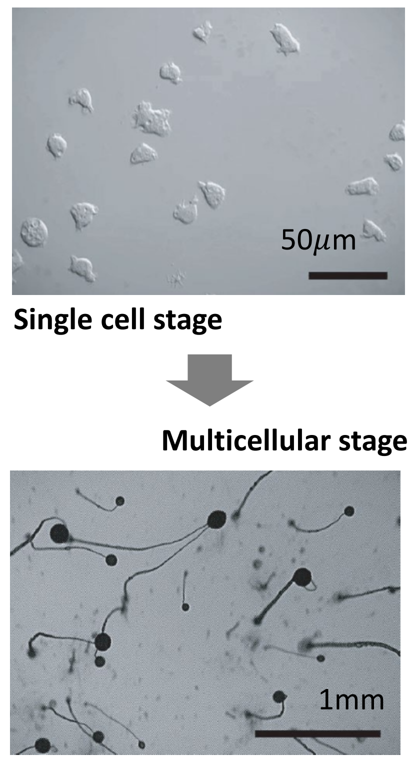
Dynamic self-organization of migrating cells

Example - Dynamic multi-cellular assemblies

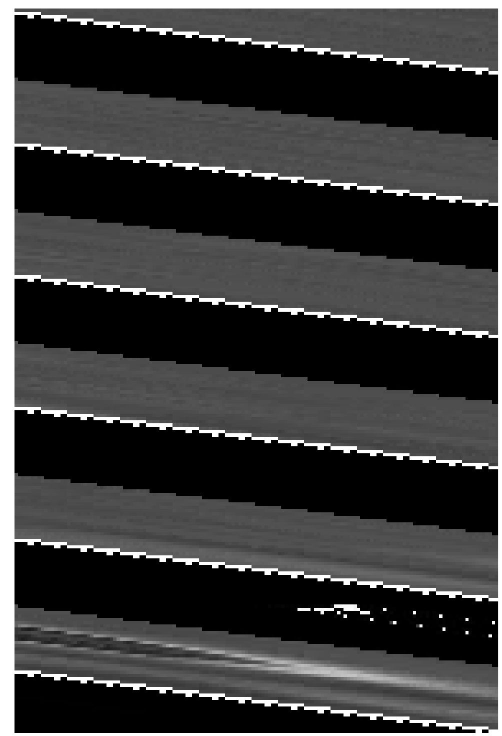
Social amoeba, *Dicty.* cell (Cellular slime mold)'s case



[http://anakin.utm.utoronto.ca/~w3oday/?section=Fruiting_Body]



Martin-Gonzalez et al. Microbial biotech. (2020)



Li et al. PLoS ONE (2008)

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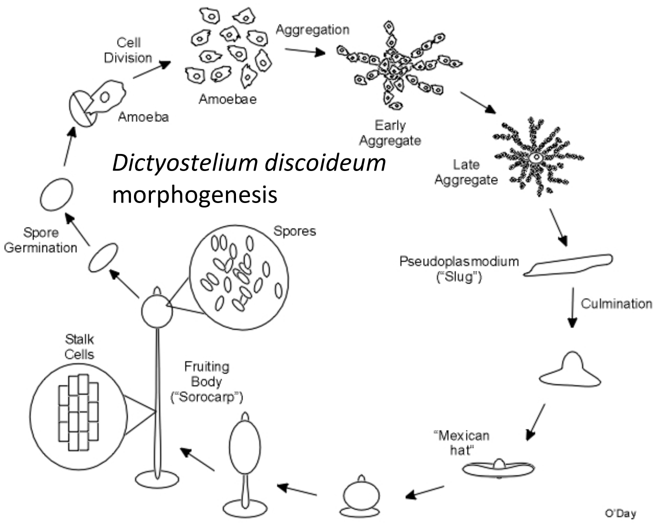
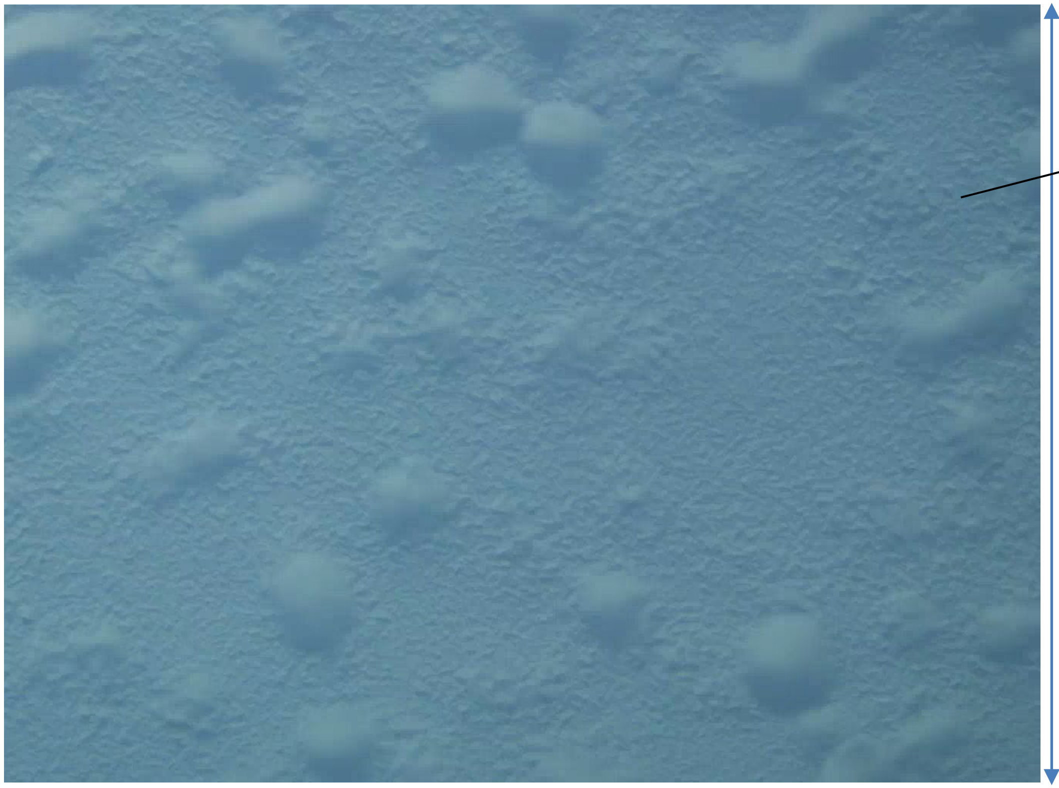


[http://anakin.utm.utoronto.ca/~w3oday/?section=Fruiting_Body]

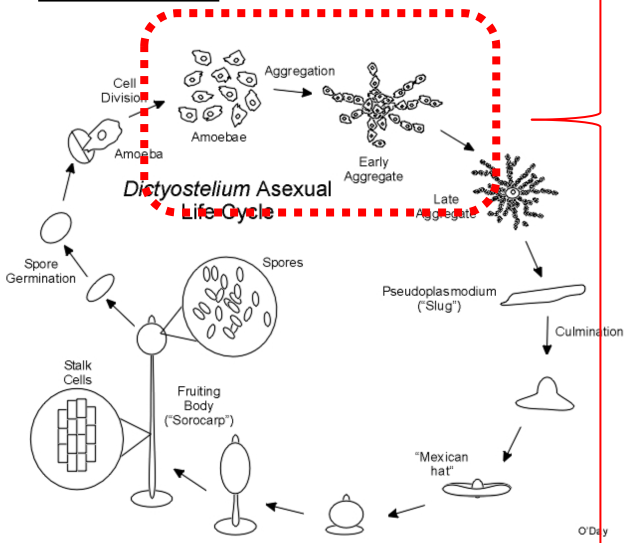


Kuwayama et al. Sci. Rep. 3, 2272 ('13)

Particular Motivation

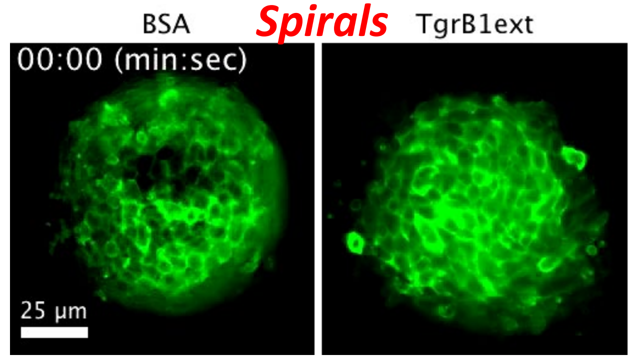
◆ Varieties of *dynamic self-organization* of migrating cells

Example.
Dictyostelium discoideum
(Dicty cells)



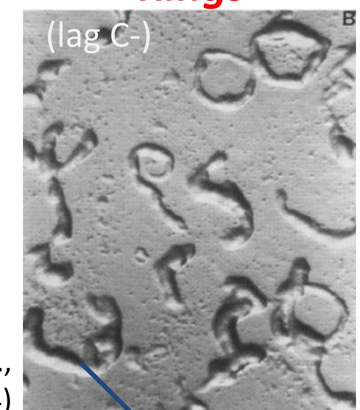
[http://anakin.utm.utoronto.ca/~w3oday/?section=Fruiting_Body]

Spirals



T. Fujimori, A. Nakajima et al.
PNAS 116, 4291 ('19)

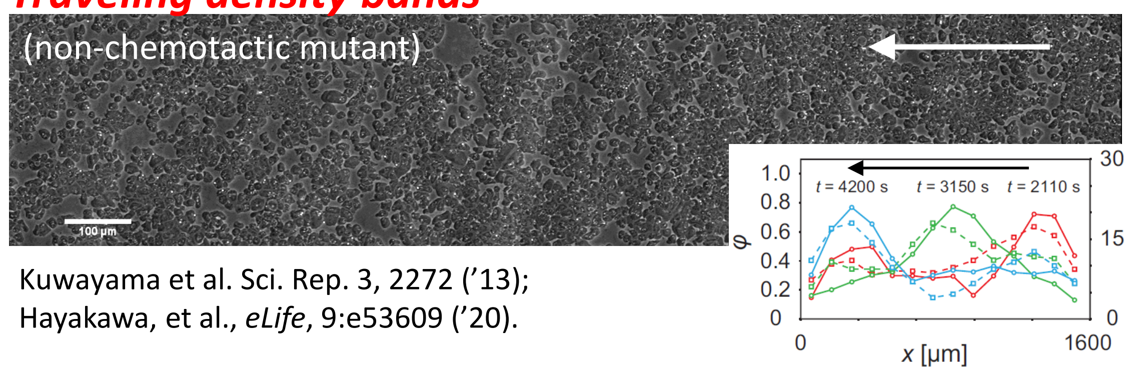
Rings



Dynes et al.,
Genes and Dev. ('94)

cluster of cells

Traveling density bands



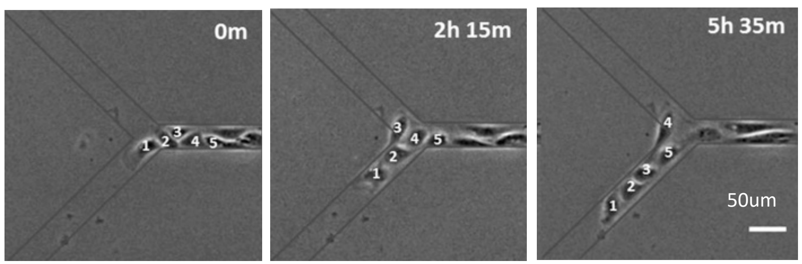
Kuwayama et al. Sci. Rep. 3, 2272 ('13);
Hayakawa, et al., *eLife*, 9:e53609 ('20).

——— φ (local order) - - - - - N (local density)

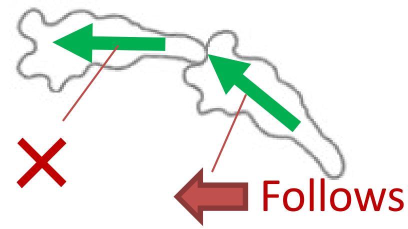
◆ **How can we explain such wide varieties of dynamic patterns?**

Example of cell-cell communication
Contact following

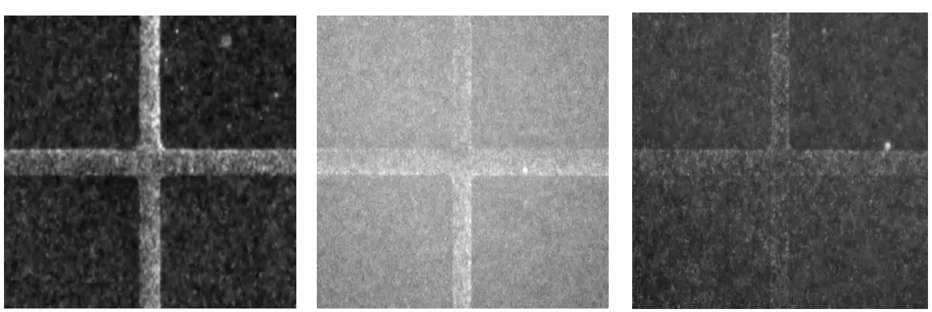
- ✓ A cell backside follows the forward, but not vise versa
  - ➢ One of ubiquitous types of cell-cell communication
  - ➢ Playing roles in forming dynamical patterns (see e.g. Fujimori et al. PNAS 116, 4291 '19)



Li and Wang PNAS (2018). (NRK-52E cells)

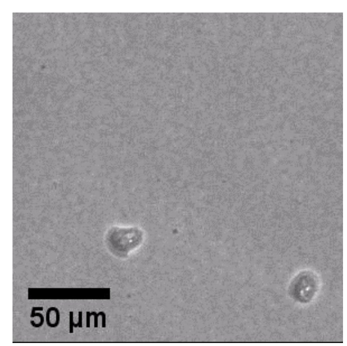


NRE-52E cells ***MDCK cells*** ***NIH-3T3 cells***

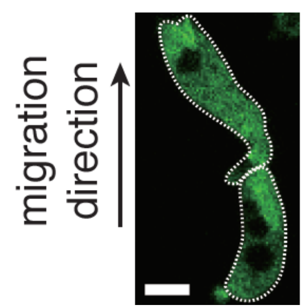


Li and Wang PNAS 2018

Dicty cells



Hayakawa et al., eLife. 2020



F-actin

Fujimori et al. PNAS 2019

<u>Aims</u>:

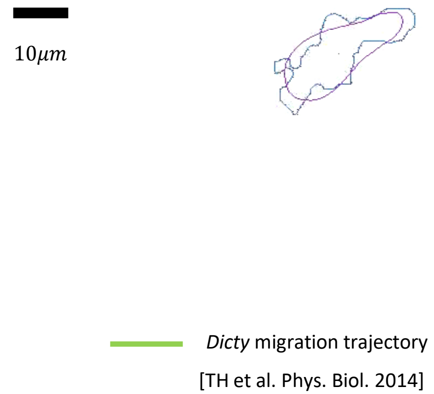
Develop a computational framework to simulate ***dynamic self-organization (DSO) of migrating cells*** through ***contact communication***

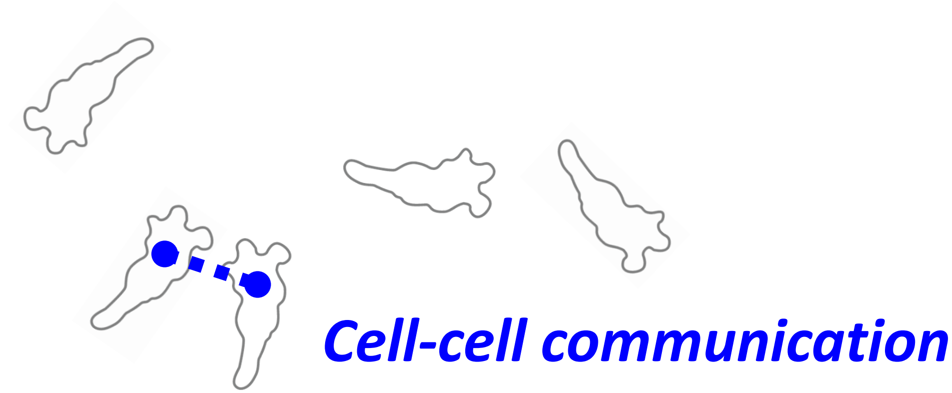
> See if this framework can reproduce wide varieties of dynamic patterns

>> demonstrate one of the principles in forming various cellular organization patterns.

<u>Method</u>:

Theoretical modeling with the individual cell dynamics-based model approach





- T. Hiraiwa, *Euro. Phys. J. E* 45, 1 (2022).
  "Dynamic self-organization … under constraints by spatial confinement and epithelial integrity"
- T. Hiraiwa, *Phys. Rev. Lett.* 125, 268104 (2020).
  "Dynamic self-organization of idealized migrating cells by contact communication"
- M. Hayakawa, T. Hiraiwa, … T. Shibata, *eLife* 9, e53609 (2020).
  "Polar pattern formation induced by contact following locomotion in a multicellular system"
- T Hiraiwa, *Phys. Rev. E.* 99, 012614 (2019).
  "Two types of exclusion interactions for self-propelled objects and collective motion induced by their combination"

Multicellular behavior

+ Cell-cell communication

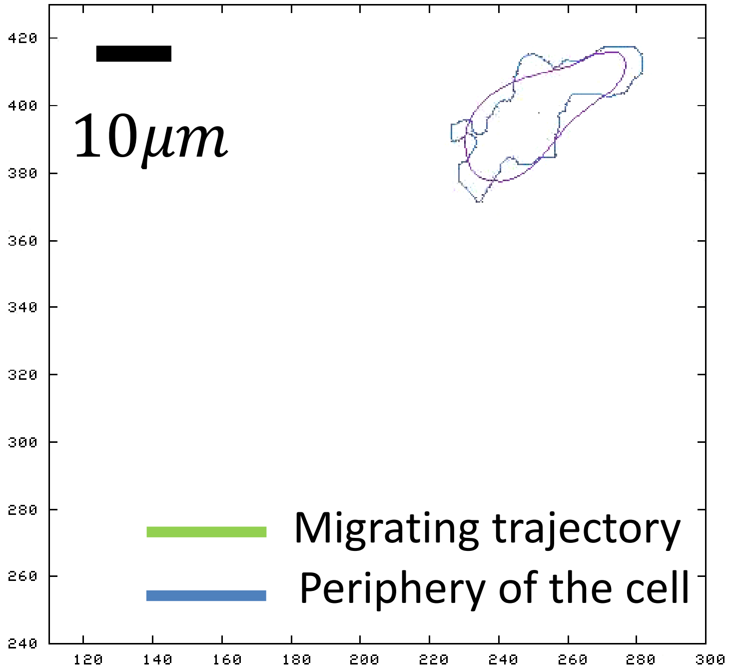
- T. Hiraiwa et al. *Physical Biology* 11, 056002 (2014).
  "Relevance of intracellular polarity to accuracy of eukaryotic chemotaxis"
- T. Hiraiwa et al., *Euro. Phys. J. E* 36 32 (2013).
  "Theoretical model for cell migration with gradient sensing and shape deformation"

Single cell migration

Motility analysis for a single cell migration

Hiraiwa et al., Phys. Biol. 11, 056002 (2014)

Trajectory of spontaneously migrating *Dicty.* (starved)

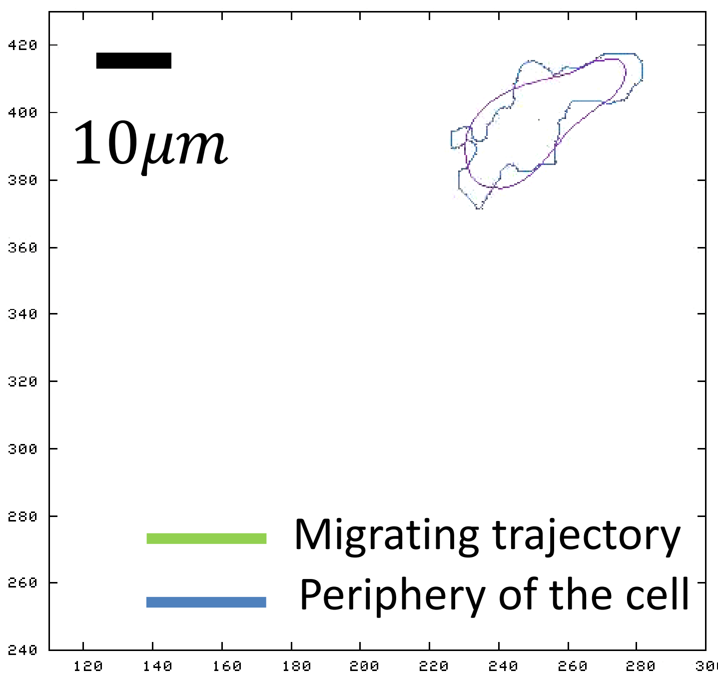


(Movie = 300secs)

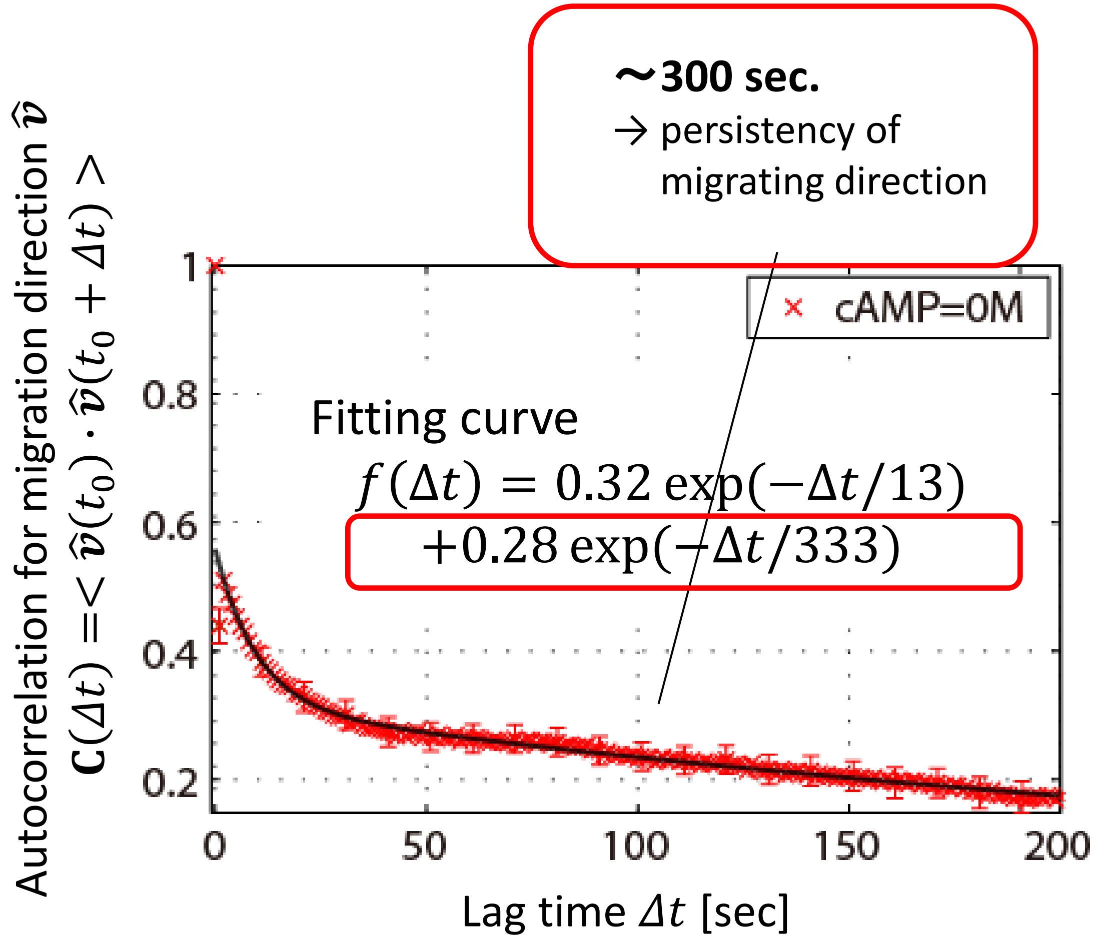
Motility analysis for a single cell migration

Hiraiwa et al., Phys. Biol. 11, 056002 (2014)

Trajectory of spontaneously migrating *Dicty.* (starved)



(Movie = 300secs)



"There is some polarity associated with motility"

Mathematical model of a single cell migration

Hiraiwa et al., Phys. Biol. 11, 056002 (2014).

$$\begin{cases} \dfrac{d}{dt}\boldsymbol{x} = \underline{\boldsymbol{F}(\boldsymbol{q})} + \underline{\boldsymbol{\xi}^x} \\ \dfrac{d}{dt}\boldsymbol{q} = \underline{\boldsymbol{M}(\boldsymbol{q})} + \underline{\boldsymbol{\xi}^{\mathrm{q}}} \end{cases}$$

Self-propulsion

e.g. $F(\boldsymbol{q}_i) = v_0 \boldsymbol{q}_i / |\boldsymbol{q}_i|$

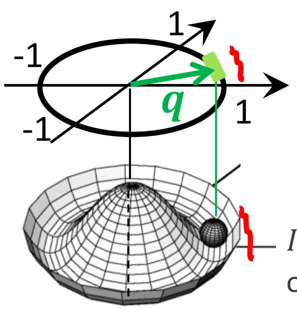
To specify the intrinsic nature of polarity

Noise term

$\boldsymbol{x}$: position of the cell ($= (x, y)$ in 2D)

$\boldsymbol{q}$: intrinsic polarity

v_s: constant velocity

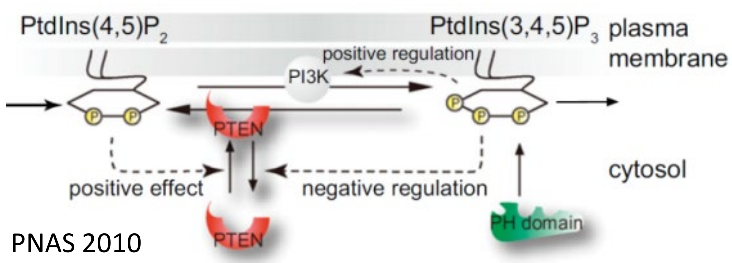


e.g. spontaneous violation of isotropy

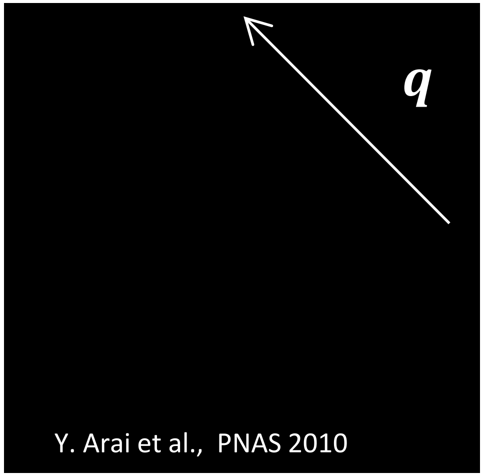
$$\boldsymbol{M}(\boldsymbol{q}) = -\partial U(\boldsymbol{q}) / \partial \boldsymbol{q}$$

$$U(\boldsymbol{q}) = I_q (1 - |\boldsymbol{q}|^2)^2$$

I_q: Constant (This talk focuses on $I_q \to \infty$ and $|\boldsymbol{q}_i| = 1$.)



Y. Arai et al., PNAS 2010



Mathematical model of a single cell migration

Hiraiwa et al., Phys. Biol. 11, 056002 (2014).

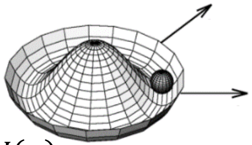
$$
\begin{cases}
\dfrac{d}{dt}\boldsymbol{x} = v_s \boldsymbol{q} \\[2ex]
\dfrac{d}{dt}\boldsymbol{q} = \underline{\boldsymbol{\xi}}
\end{cases}
$$

Gaussian white noise

$\boldsymbol{x}$: position of the cell ($=(x, y)$ in 2D)
$\boldsymbol{q}$: intrinsic polarity
v_s: constant velocity

under the constraint $|\boldsymbol{q}| = 1$

(assuming $I_q \to \infty$ for simplicity)



$U(\boldsymbol{q}) = I_q(1 - |\boldsymbol{q}|^2)^2$

Mathematical model of a single cell migration

Hiraiwa et al., Phys. Biol. 11, 056002 (2014).

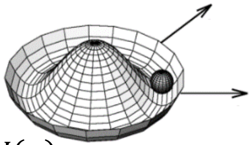
$$\begin{cases} \dfrac{d}{dt}\boldsymbol{x} = v_s \boldsymbol{q} \\ \dfrac{d}{dt}\boldsymbol{q} = \underline{\boldsymbol{\xi}} \end{cases}$$

Gaussian white noise

$\boldsymbol{x}$: position of the cell ($= (x, y)$ in 2D)
$\boldsymbol{q}$: intrinsic polarity
v_s: constant velocity

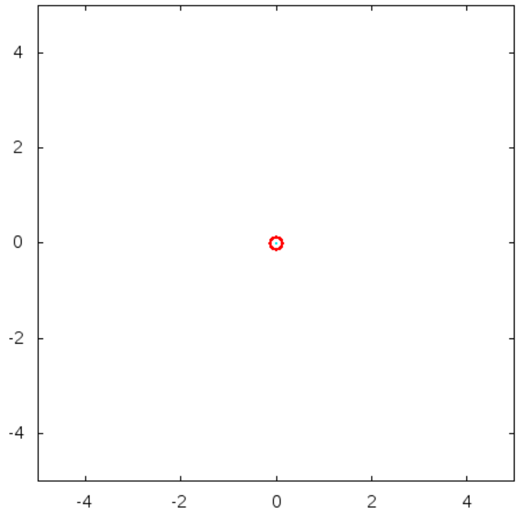
under the constraint $|\boldsymbol{q}| = 1$

(assuming $I_q \to \infty$ for simplicity)

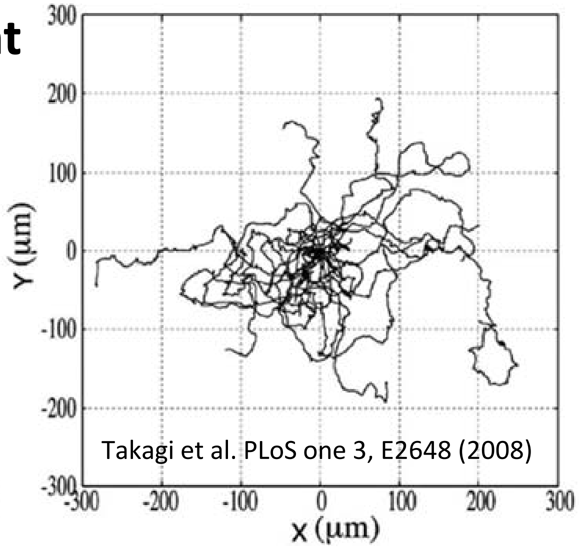


$U(\boldsymbol{q}) = I_q(1 - |\boldsymbol{q}|^2)^2$

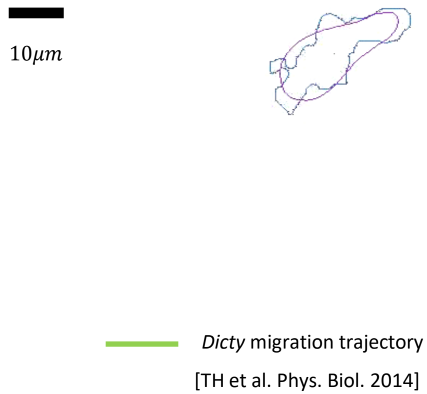
Simulation

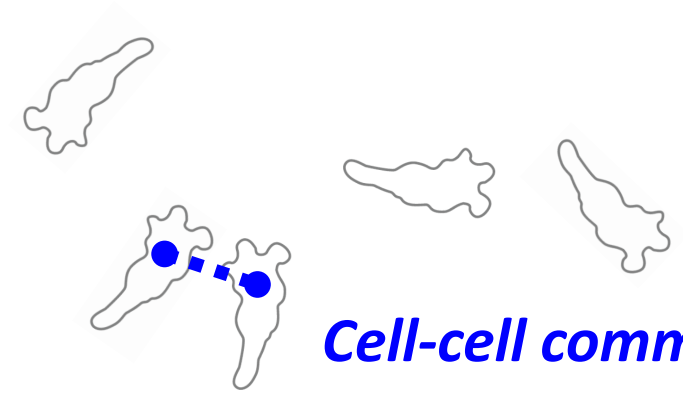


Experiment



Takagi et al. PLoS one 3, E2648 (2008)





Cell-cell communication

Multicellular behavior

- T. Hiraiwa, *Euro. Phys. J. E* 45, 1 (2022).
  "Dynamic self-organization … under constraints by spatial confinement and epithelial integrity"
- T. Hiraiwa, *Phys. Rev. Lett.* 125, 268104 (2020).
  "Dynamic self-organization of idealized migrating cells by contact communication"
- M. Hayakawa, T. Hiraiwa, … T. Shibata, *eLife* 9, e53609 (2020).
  "Polar pattern formation induced by contact following locomotion in a multicellular system"
- T Hiraiwa, *Phys. Rev. E.* 99, 012614 (2019).
  "Two types of exclusion interactions for self-propelled objects and collective motion induced by their combination"

+ Cell-cell communication

- T. Hiraiwa et al. *Physical Biology* 11, 056002 (2014).
  "Relevance of intracellular polarity to accuracy of eukaryotic chemotaxis"
- T. Hiraiwa et al., *Euro. Phys. J. E* 36 32 (2013).
  "Theoretical model for cell migration with gradient sensing and shape deformation"

Single cell migration

Generic framework for numerical simulation

✓ **Dynamics of positions x_i (i=1,2,…,N)**

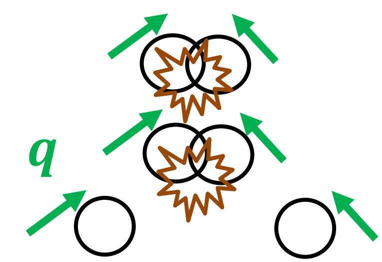
$$\Xi^v(\boldsymbol{q}_i)\frac{d}{dt}\boldsymbol{x}_i = \boldsymbol{F}(\boldsymbol{q}_i) + \xi_i^x + \boldsymbol{K}_i(\{\boldsymbol{x}_j\})$$

"friction" tensor

Self-propulsion

e.g. $F(\boldsymbol{q}_i) = v_0\boldsymbol{q}_i/|\boldsymbol{q}_i|$

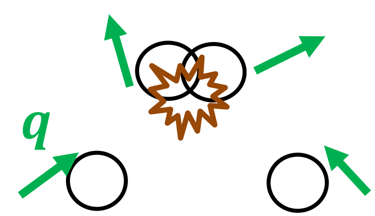
$\boldsymbol{K}_i$: Positional interaction

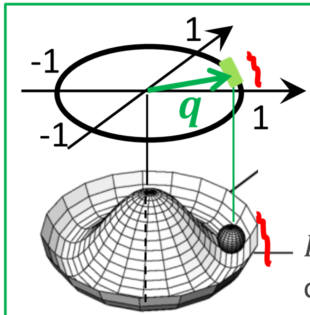


✓ **Dynamics of polarity q_i (i=1,2,…,N)**

$$\Xi^q(\boldsymbol{q}_i)\frac{d}{dt}\boldsymbol{q}_i = \boldsymbol{M}_i + \xi_i^q + \boldsymbol{L}_i(\{\boldsymbol{x}_j\})$$

$\boldsymbol{L}_i$: Directional interaction





e.g. spontaneous violation of isotropy

$\boldsymbol{M}_i(\boldsymbol{q}_i) = -\partial U(\boldsymbol{q}_i)/\partial \boldsymbol{q}_i$

$U(\boldsymbol{q}_i) = I_q(1-|\boldsymbol{q}_i|^2)^2$

I_q: Constant (This talk focuses on $I_q \to \infty$ and $|\boldsymbol{q}_i| = 1$.)

To specify the intrinsic nature of polarity

Noise term

✓ **(+ if needed, more dynamic equations for higher-order tensors)**

In general, far-from-equilibrium

- ***No FDT***
- ***No single variational function (Non reciprocality)***

Hiraiwa, Phys Rev E 99, 012614 ('19)

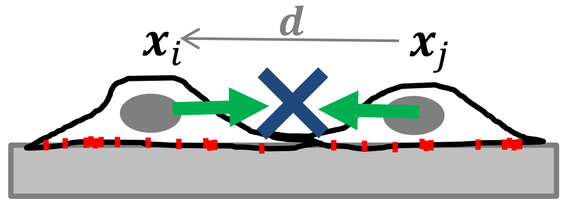
Simplest case for migrating cells

Dynamics of position (i-th cell, i=1,2,…,N)

$$\frac{d}{dt}\boldsymbol{x}_i = v_s \boldsymbol{q}_i + \boldsymbol{K}_i(\{\boldsymbol{x}_j\})$$

v_s: constant speed of migration

Mechanical interaction
(Assume **volume exclusion** here)



$$\boldsymbol{K}_i(\{\boldsymbol{x}_j\}) = -\beta \sum_{j:\,|d_{ij}|<r} \left[\frac{r\boldsymbol{d}_{ij}}{|\boldsymbol{d}_{ij}|^2} - 1\right]$$

with $\boldsymbol{d}_{ij} = \boldsymbol{x}_i - \boldsymbol{x}_j$

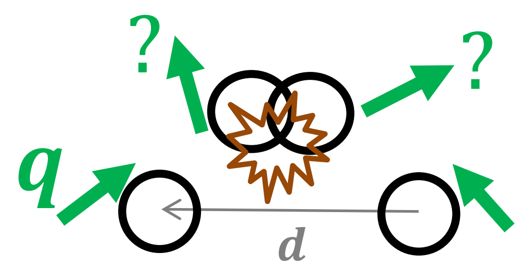
Dynamics of polarity (i-th cell, i=1,2,…,N)

$$\frac{d}{dt}\boldsymbol{q}_i = \xi_i + \boldsymbol{L}_i(\{\boldsymbol{x}_j\})$$

with the constraint $|\boldsymbol{q}_i| = 1$

ξ_i: Noise term
(White Gaussian)

Certain cell-cell communication

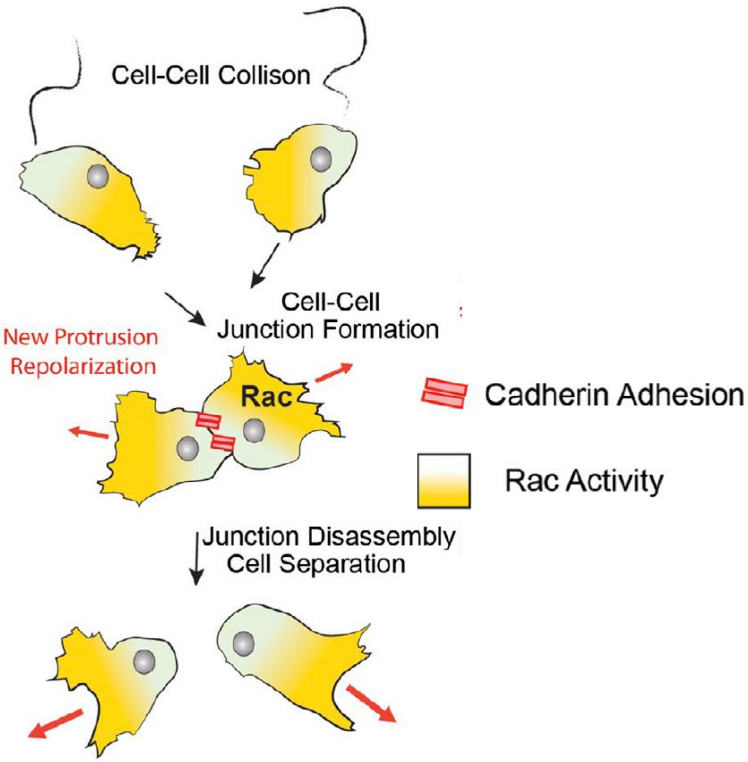


$L_i(\{\boldsymbol{x}_j\})$ = Given function

This framework was applied so far to: ***1. Contact Inhibition/Attraction of Locomotion (CIL/CAL)***
2. Contact Following **(CF)**

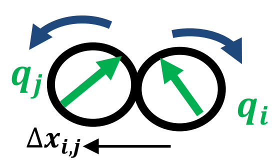
Example of contact communication
- ***Contact inhibition of locomotion***

Contact Inhibition of Locomotion (CIL)

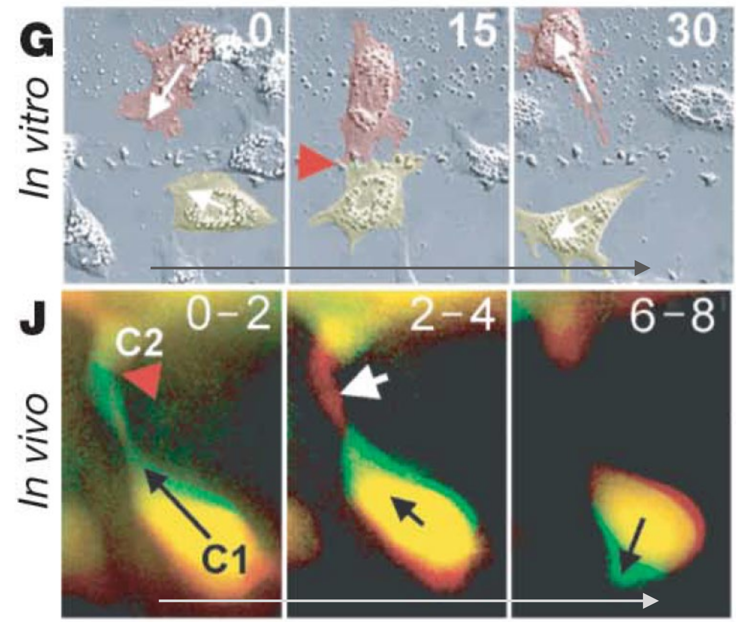


Scarpa et al. J Cell Biol. 212, 143 ('16)
(※ Xenopus's case)

$$L_i(\{x_j\}) = -\alpha_{\mathrm{CIL}} \sum_{j:\,|x_j - x_i| < r} \left(\frac{r}{|\Delta x_{i,j}|} - 1\right) \frac{\Delta x_{i,j}}{|\Delta x_{i,j}|}$$

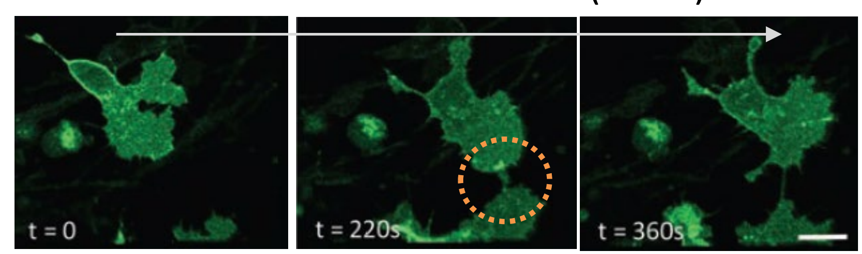


Xenopus neural crest cells



Carmona-Fontaine et al., Nature. 456, 957 ('08)

Chick neural crest cells (trunk)



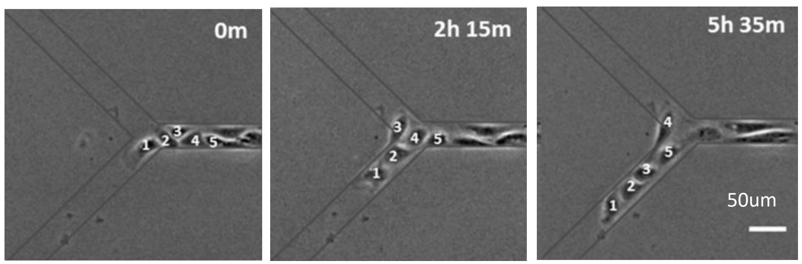
Li et al. Cell Rep. 26, 1489 '19

5um

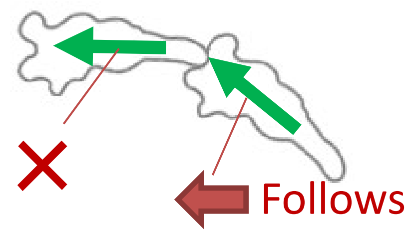
Example of contact communication - ***Contact following***

✓ A cell backside follows the forward, but not vise versa

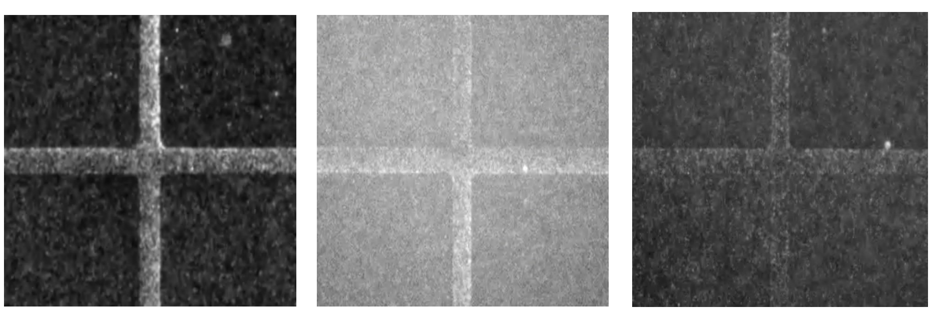
- ➢ One of ubiquitous types of cell-cell communication
- ➢ Playing roles in forming dynamical patterns (see e.g. Fujimori et al. PNAS 116, 4291 ‘19)



Li and Wang PNAS (2018). (NRK-52E cells)

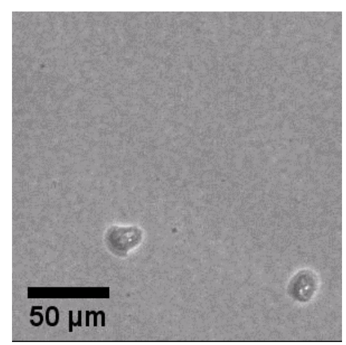


NRE-52E cells ***MDCK cells*** ***NIH-3T3 cells***

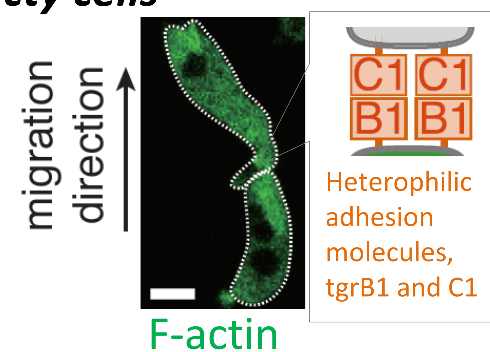


Li and Wang PNAS 2018

Dicty cells

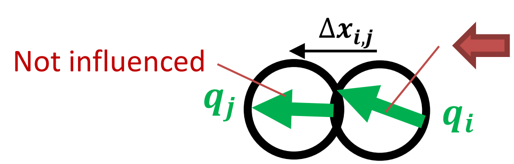


Hayakawa et al., eLife. 2020



Fujimori et al. PNAS 2019

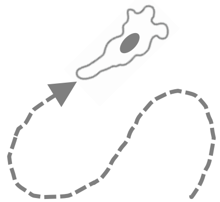
$$L_i(\{x_j\}) = \alpha_{\mathrm{CF}} \sum_{j:\, |x_j - x_i| < r} \frac{1}{2}\left(1 + q_j \cdot \frac{\Delta x_{i,j}}{|\Delta x_{i,j}|}\right) \frac{\Delta x_{i,j}}{|\Delta x_{i,j}|}$$



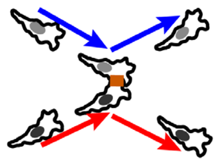
Dynamic patterns resulted by computer simulations

Hiraiwa, *Phys. Rev. Lett.* 125, 268104 (2020).

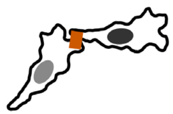
Mathematical modelling and numerical simulation



Migration

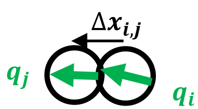


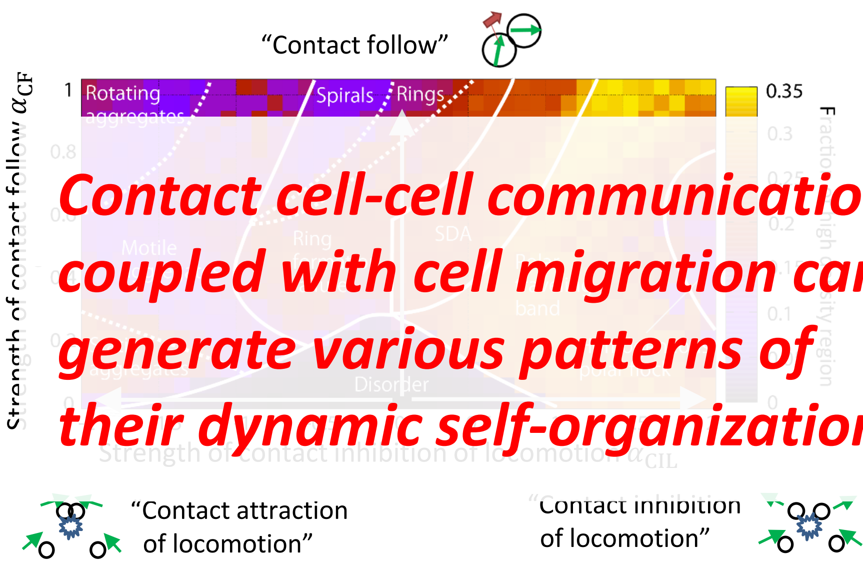
Contact Inhibition of Locomotion (CIL)



Contact Follow (CF)

$$L_i(\{x_j\}) = \alpha_{\mathrm{CF}} \sum_{j:\,|x_j - x_i| < r} \frac{1}{2}\left(1 + q_j \cdot \frac{\Delta x_{i,j}}{|\Delta x_{i,j}|}\right) \frac{\Delta x_{i,j}}{|\Delta x_{i,j}|} - \alpha_{\mathrm{CIL}} \sum_{j:\,|x_j - x_i| < r} \left(\frac{r}{|\Delta x_{i,j}|} - 1\right) \frac{\Delta x_{i,j}}{|\Delta x_{i,j}|}$$



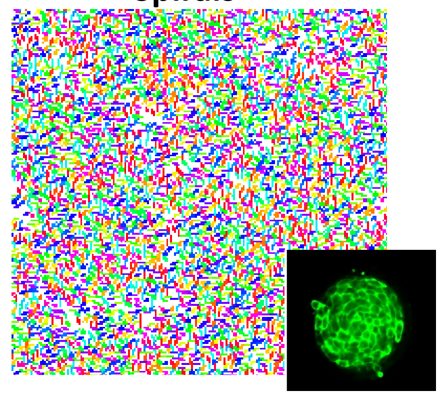


Contact cell-cell communication coupled with cell migration can generate various patterns of their dynamic self-organization

Simulation results

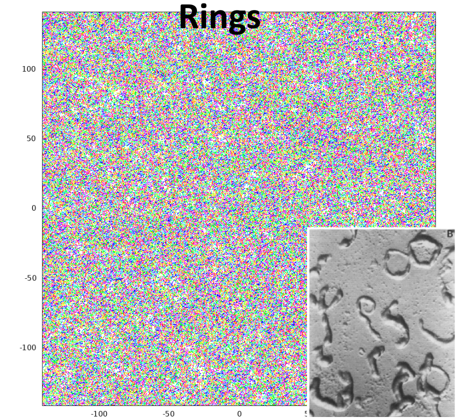
(various strengths of two types of cell-cell communication)

Spirals



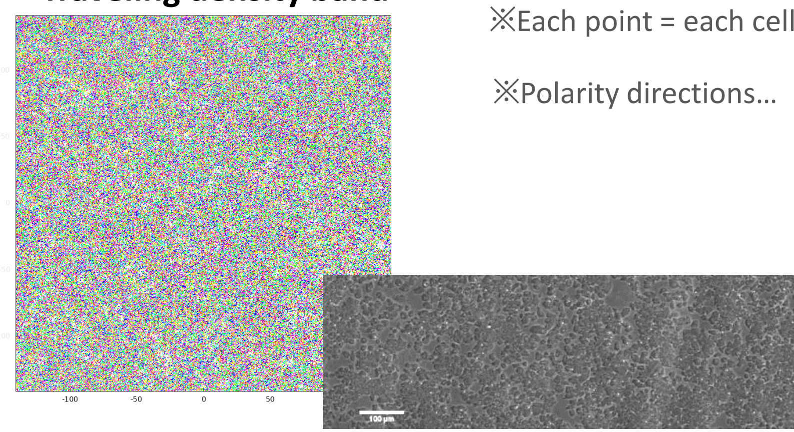
Dicty cell observation
[T. Fujimori, et al. PNAS '19]

Rings



Dicty cell observation
[J. Dynes et al., Gen. Dev. '94]

Traveling density band

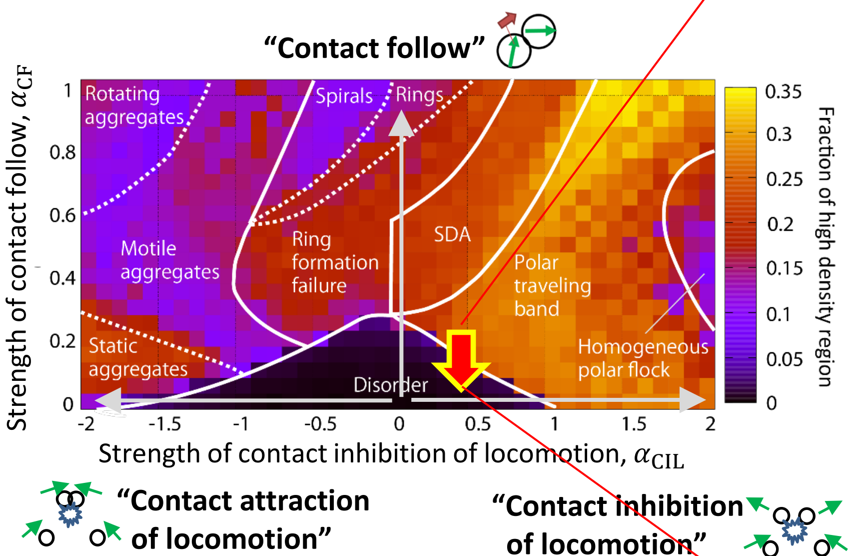


Dicty cell observation
[M. Hayakawa, T. Hiraiwa et al. *eLife* 9, e53609 '20.]

※Each point = each cell

※Polarity directions...

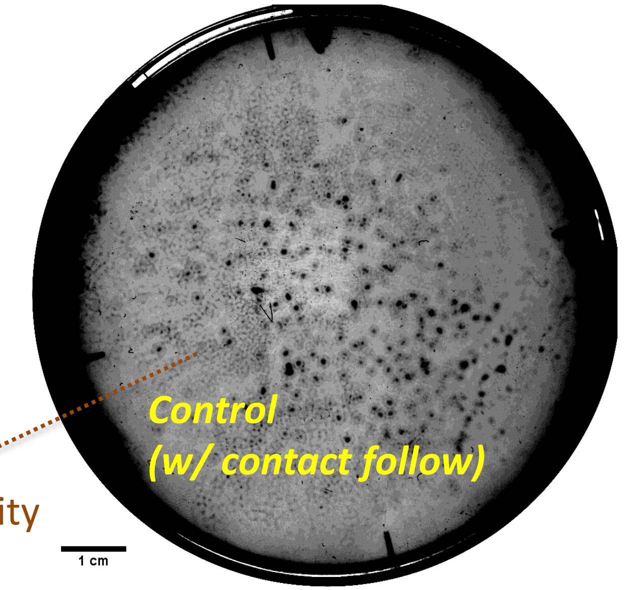
Traveling density bands in *Dicty* cells: Perturbation

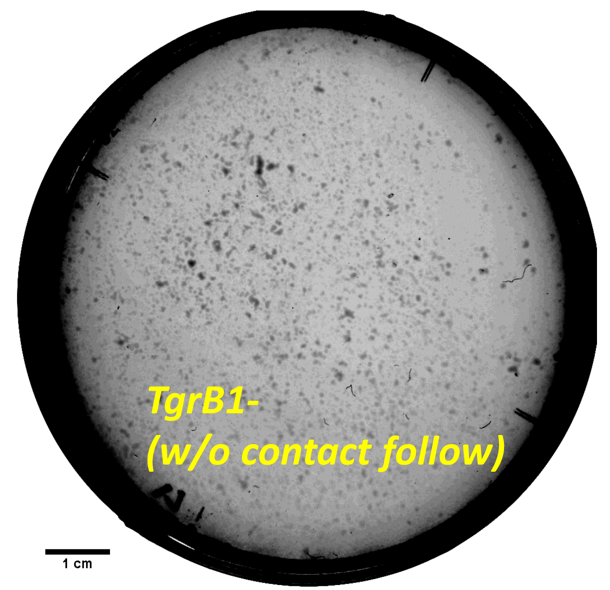


Traveling density band

No pattern

Dark region = High cell density

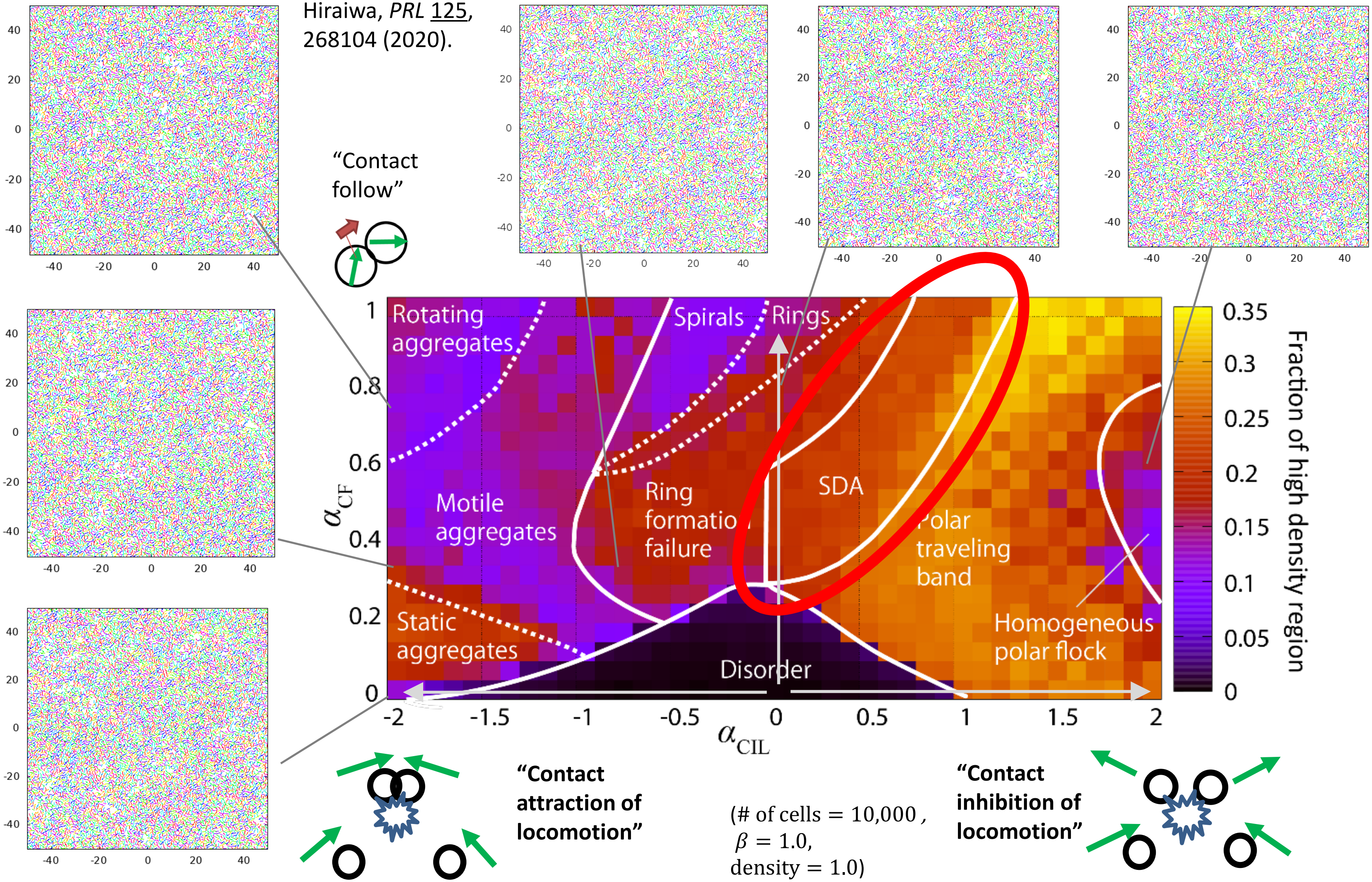




Hayakawa, Hiraiwa, …, Shibata, *eLife*. 9, e53609 (2020)

More patterns of dynamic self-organization

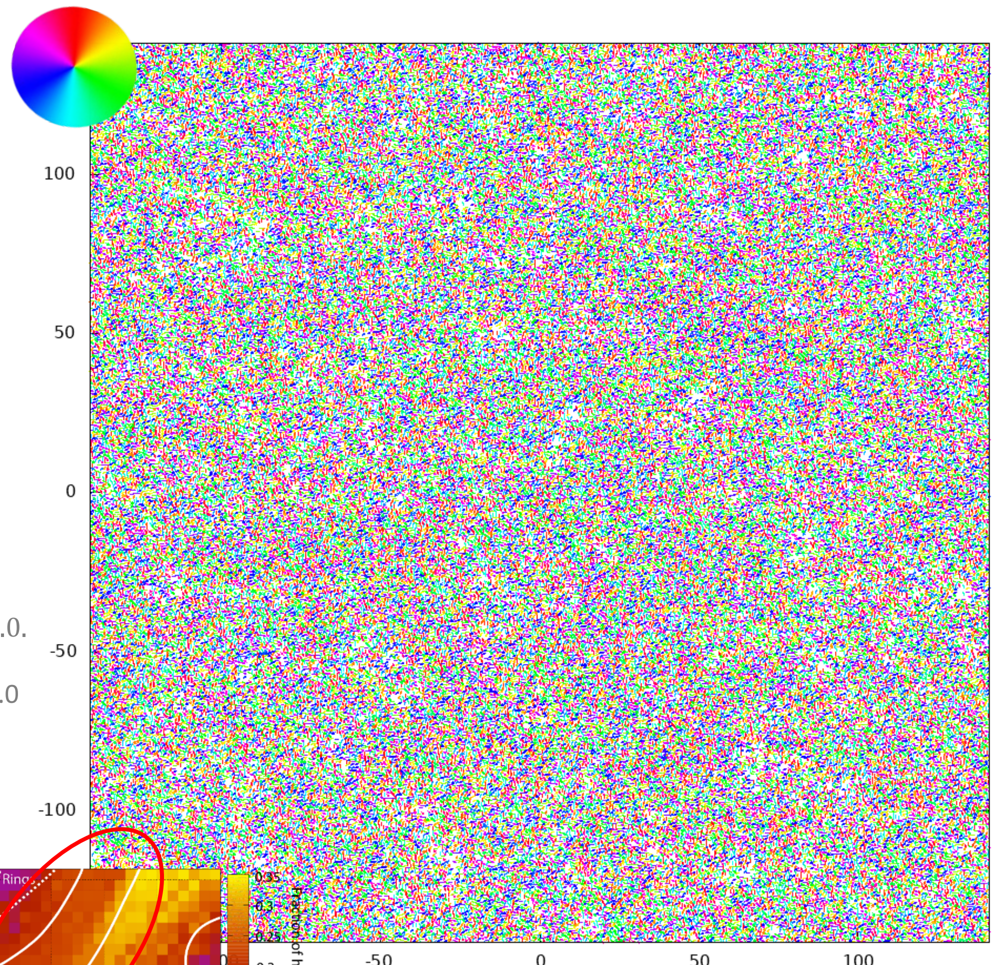
Hiraiwa, *PRL* 125, 268104 (2020).



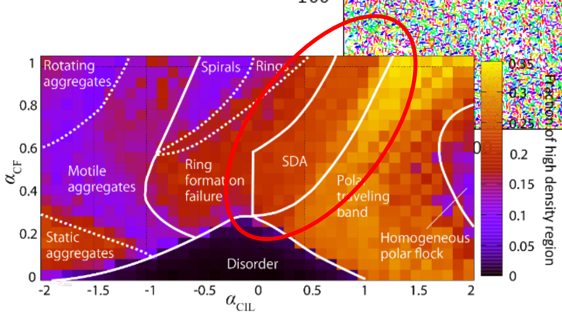
(# of cells = 10,000 , β = 1.0, density = 1.0)

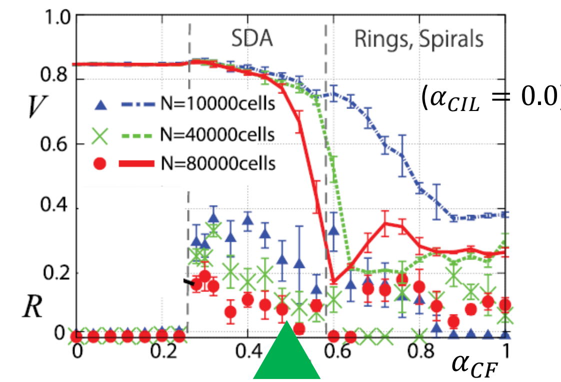
Snake-like Dynamic Assemblies (SDA)
— a new collective migration mode

Hiraiwa, *PRL* 125, 268104 (2020).



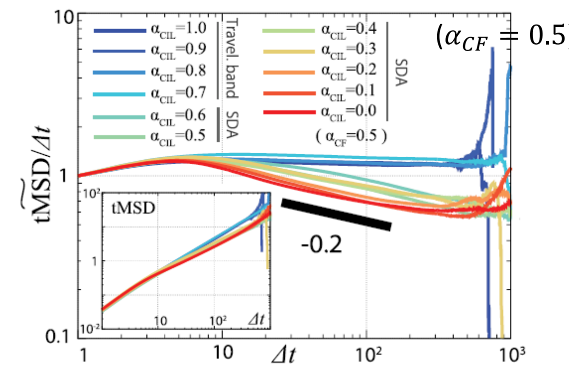
$\alpha_{CF} = 0.5, \alpha_{CIL} = 0.0.$
$\beta = 1.0$, D = 0.1,
Migration speed = 1.0
density = 1.0,
# of cells = 80,000,
cell diameter = 1.0



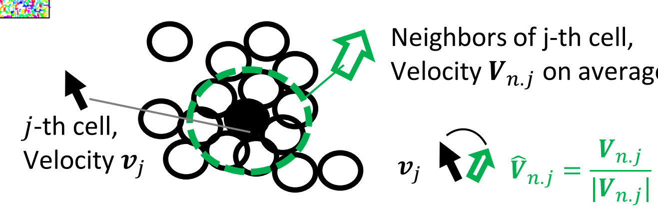


V: Median speed R: Polar order parameter

$$R = |\sum_{j=1}^{N} \boldsymbol{q}_j / N|$$



$$\mathrm{tMSD}(\Delta t) \equiv \overline{|\int_0^{\Delta t} dt' \hat{\boldsymbol{V}}_{n.j}(t_0 + t') \times \boldsymbol{v}_j(t_0 + t')|^2}$$



<u>Aims</u>:

Develop a computational framework to simulate ***dynamic self-organization (DSO) of migrating cells*** through ***contact communication***

> See if this framework can reproduce wide varieties of dynamic patterns

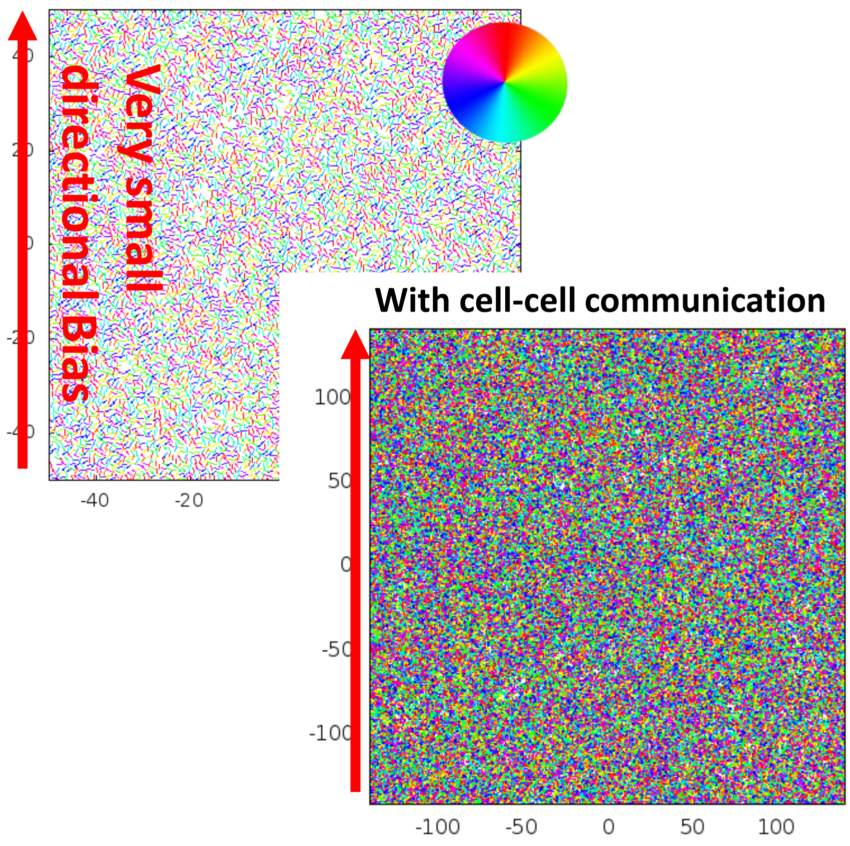
>> demonstrate one of the principles in forming various cellular organization patterns.

Contact cell-cell communication coupled with ***cell migration*** can generate various patterns of their dynamic self-organization

Toward studies of functional roles of DSO in living organisms

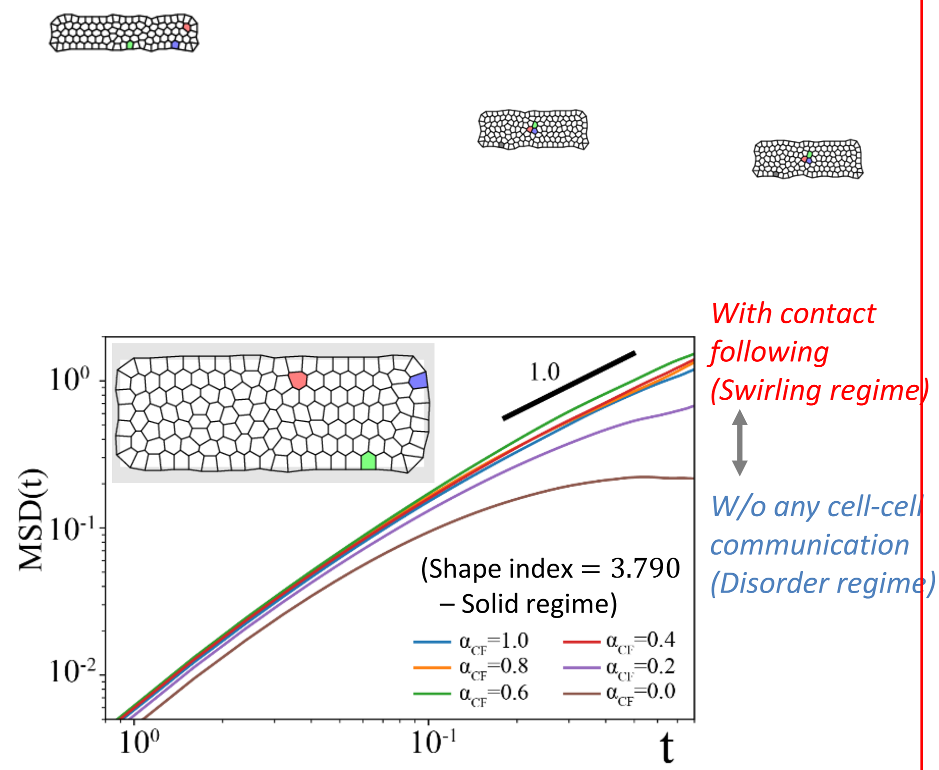
Role of DSO for directional (taxis) migration

Without cell-cell communication



Hiraiwa, *PRE* 99, 012614 (2019);
PRL 125, 268104 (2020).

Role of DSO for migration under constraints



Hiraiwa, EPJE Topical Issue "Tissue Mechanics", 45, 1 (2022).

Brief summary of this part

- Dynamic self-organization (DSO) of migrating cells through contact cell-cell communication

- Our simulation demonstrated one of the fundamental mechanisms to produce variety of cellular DSO
  ー *Cell-cell contact communication combined with random motion of each cell*

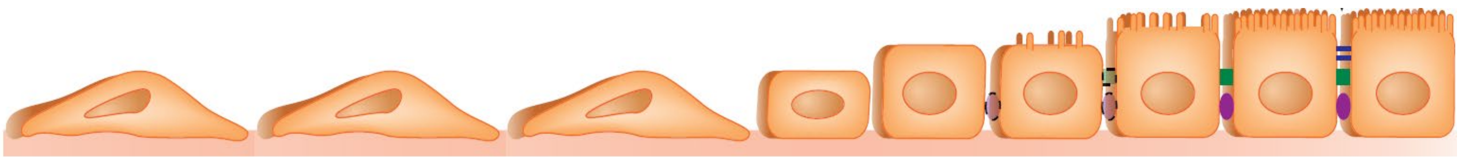
- DSO can (1) enhance collective taxis ability, and (2) help cells overcome the constraint due to their mechanical integrity.

TH, A. Baba, T. Shibata, Euro. Phys. J. E 36, 32 ('13). *TH et al. Phys. Biol. 11, 056002 ('14).* *TH, Phys. Rev. E, 99, 012614 ('19).*
M. Hayakawa, TH et al., eLife 9, e53609 ('20). ***TH, Phys. Rev. Lett. 125, 268104 ('20).*** ***TH, Euro. Phys. J. E 45, 1 ('22).***

Table of contents

- Introduction
- Dynamic self-organization of migrating cells
- Collective motion of active matter, and the gliding assay’s case
- Other works and future plan

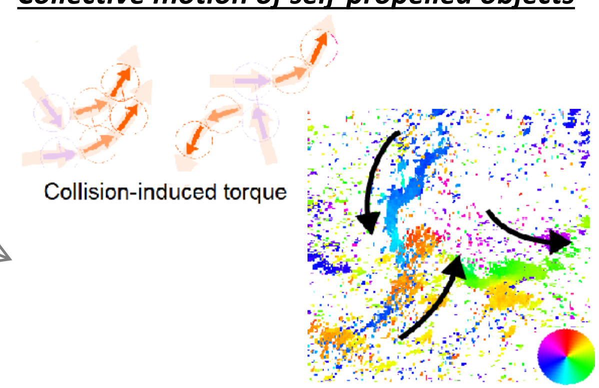
Theoretical studies on (dynamic) self-organization in living organisms and active matter



Cells and cell collectives as **“active matter”.**

Ex. of collaborations with external groups

<u>Collective motion of self-propelled objects</u>

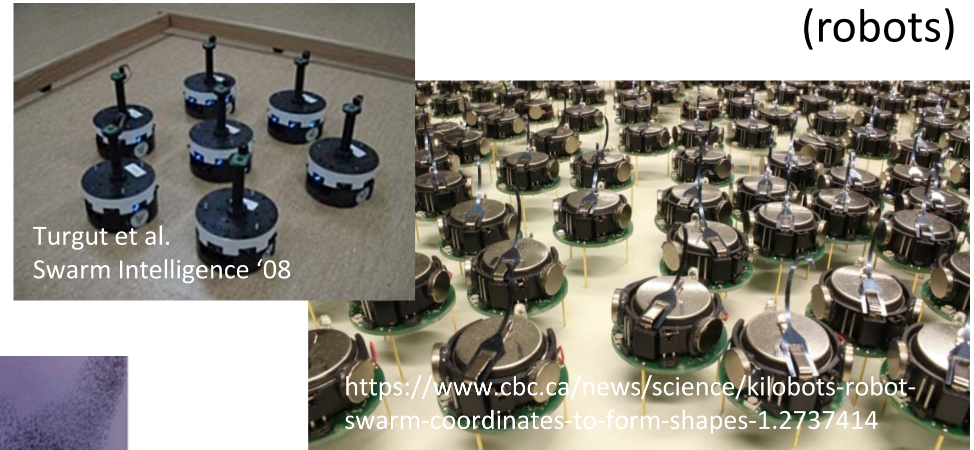


Hiraiwa, Akiyama et al. *Phys. Chem. Chem. Phys.* (2022).

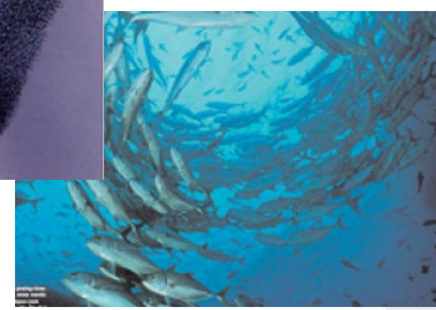
Top figure: Adapted from : https://www.mechanobio.info/development/what-is-the-epithelial-to-mesenchymal-transition-emt/

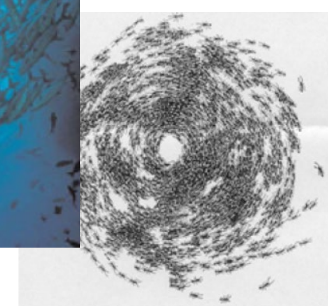
Wide varieties of collective motion in nature

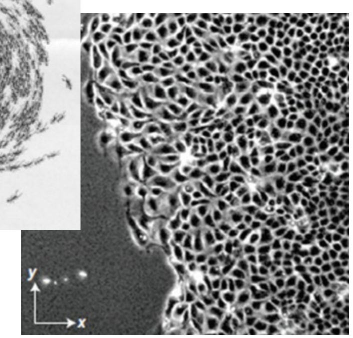
(robots)



"kilobot" Rubenstein et al. IEEE '12





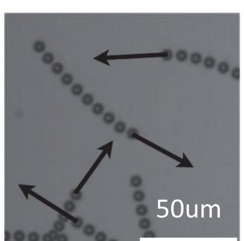


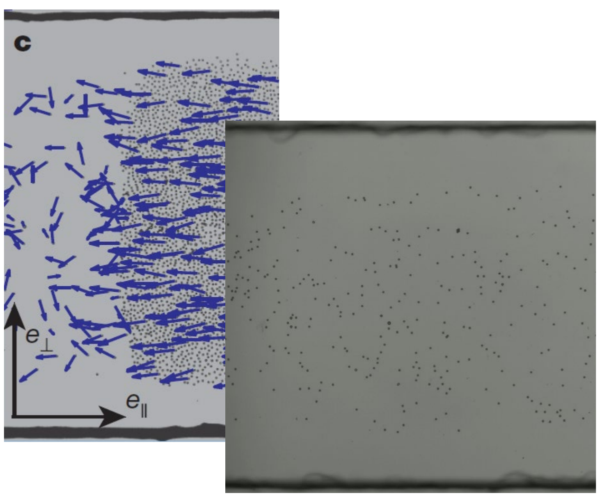
From a review article:
T. Vicsek, A. Zafeiris,
Phys. Rep. <u>517</u>, 71–140 (2012)

(Migrating cells)

(colloids)

Bricard et al.
Nature '13

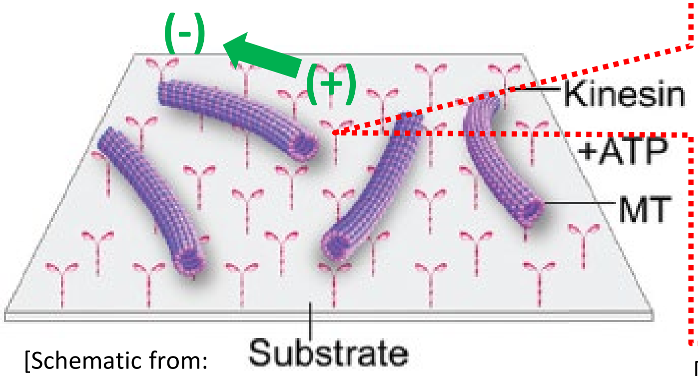




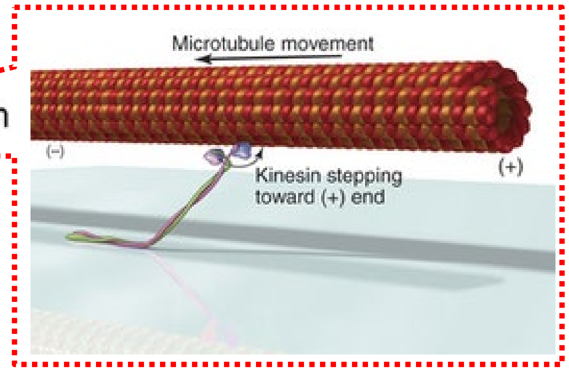
<u>Collective motion in/of active matter</u>

Collective motion patterns in biofilament gliding assays

Microtubules on kinesin-coated substrate

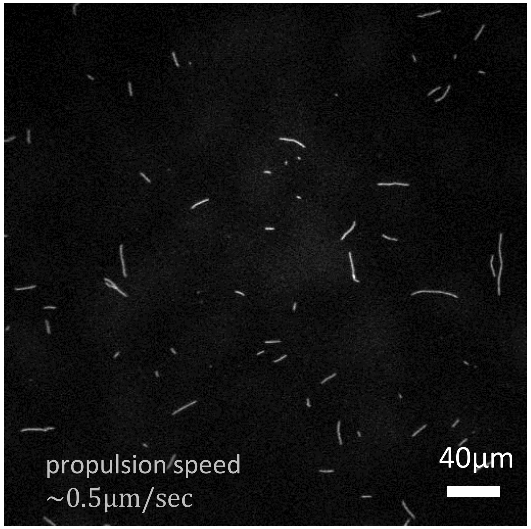


[Schematic from:
T. Munmun et al.,
Chem. Commun. 56, 1187 ('20).]

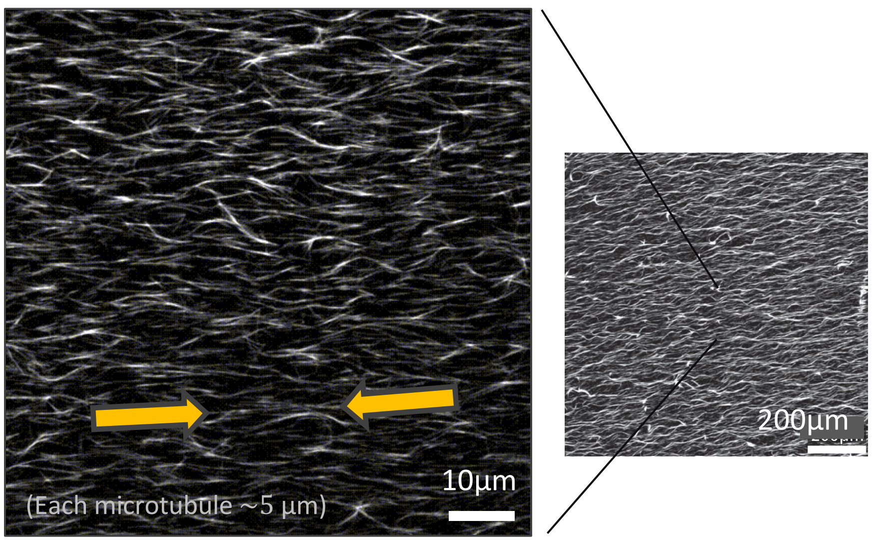


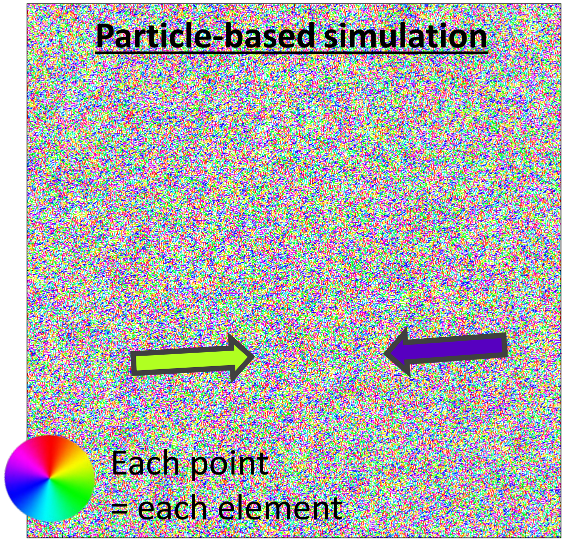
[Schematic from:
https://basicmedicalkey.com/
motor-proteins/]

[K. Kim, et al.
Soft Matter '18]



Collective motion

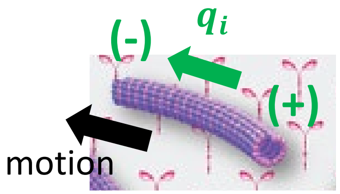




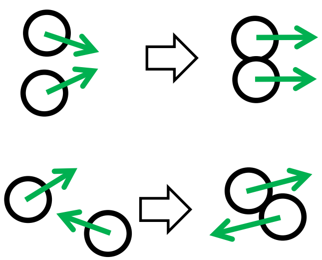
*Tanida, …, **Hiraiwa**, …, Sano (2020): Phys. Rev. E*

Collective motion in microtubule gliding assay

intrinsic polarity

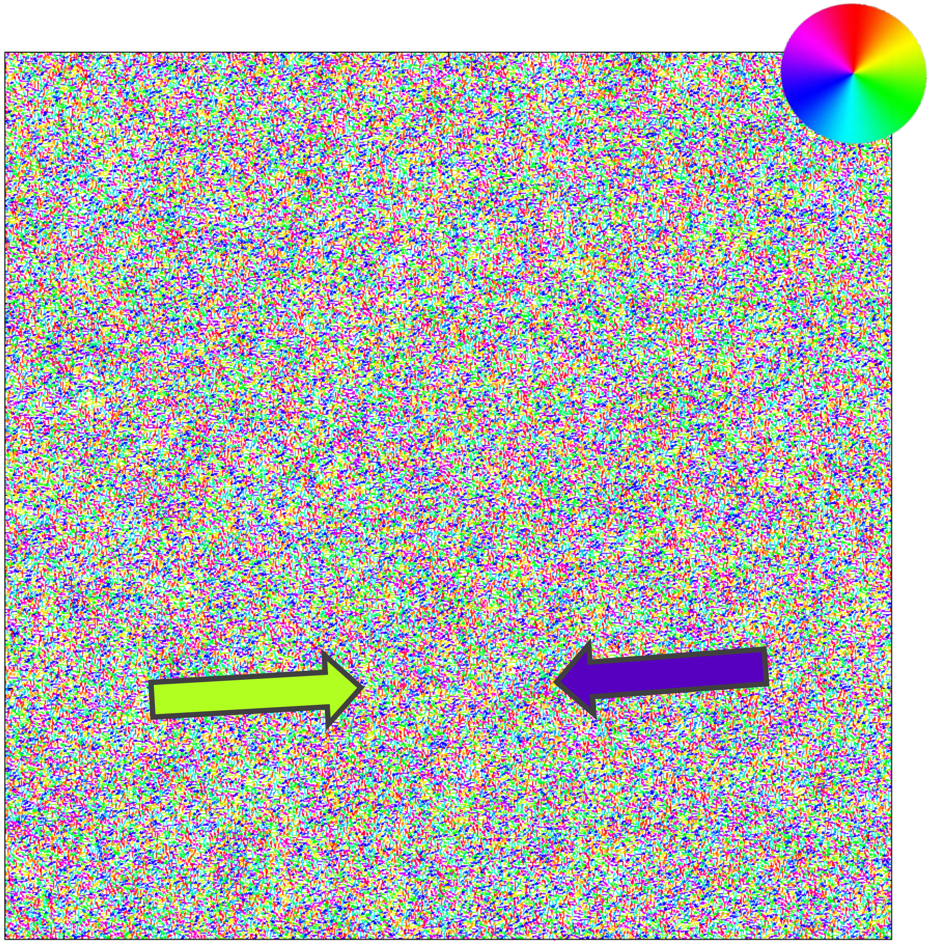


Bi-dir. alignment

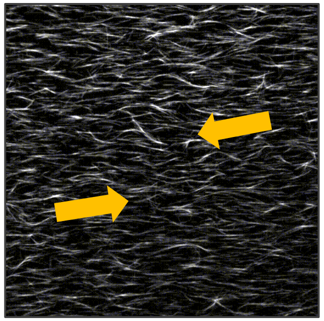


Each object tends to redirect to the (anti-)parallel direction of its neighbors

$L_i = \alpha_{AL} \sum_{j:\,|d_{ij}|<r} (q_i \cdot q_j) q_j$



Microtubule Ggiding assay



v_0: Constant speed,

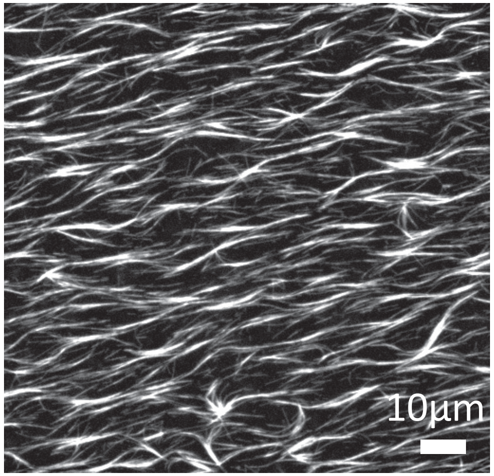
(1) Eqs. of motions of objects i=1,…,N (at the positions $\boldsymbol{x_i}$, resp.) : $\frac{d}{dt}\boldsymbol{x_i} = v_0 \boldsymbol{q_i}$

(2) Dynamics of directionality (polarity) q_i : $\frac{d}{dt}\boldsymbol{q}_i = \boldsymbol{L}_i + \boldsymbol{\xi}_i$ with $|\boldsymbol{q}_i| = 1$

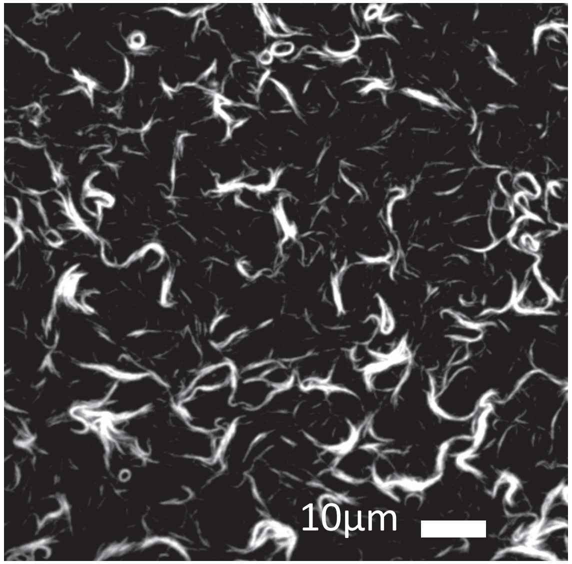
Random disturbance (White Gaussian noise)

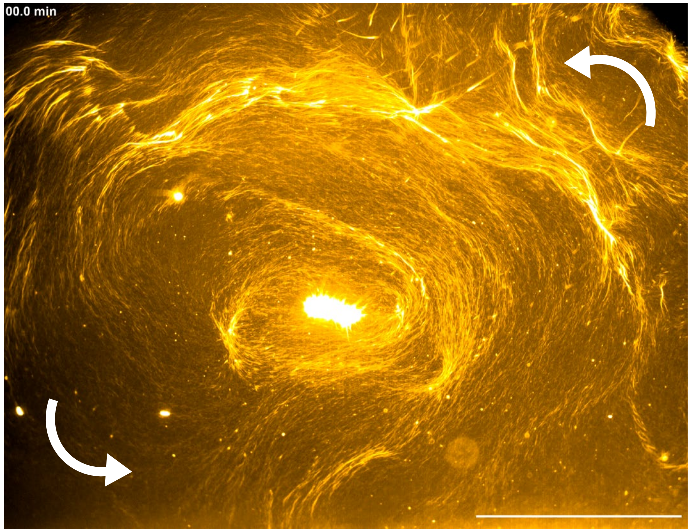
Spontaneously formed, and well maintained

Varieties of self-organization patterns



Tanida, …, Hiraiwa, … Sano,
PRE 101, 032607 ('20)

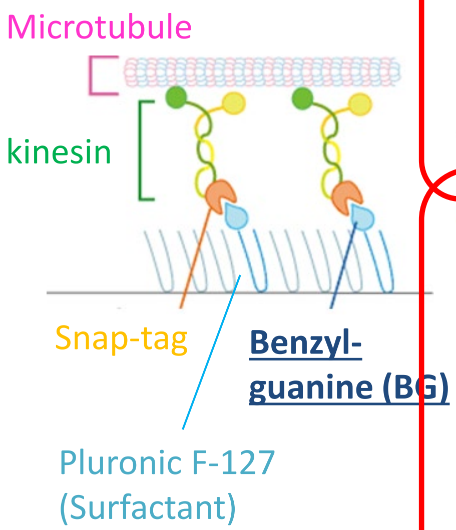


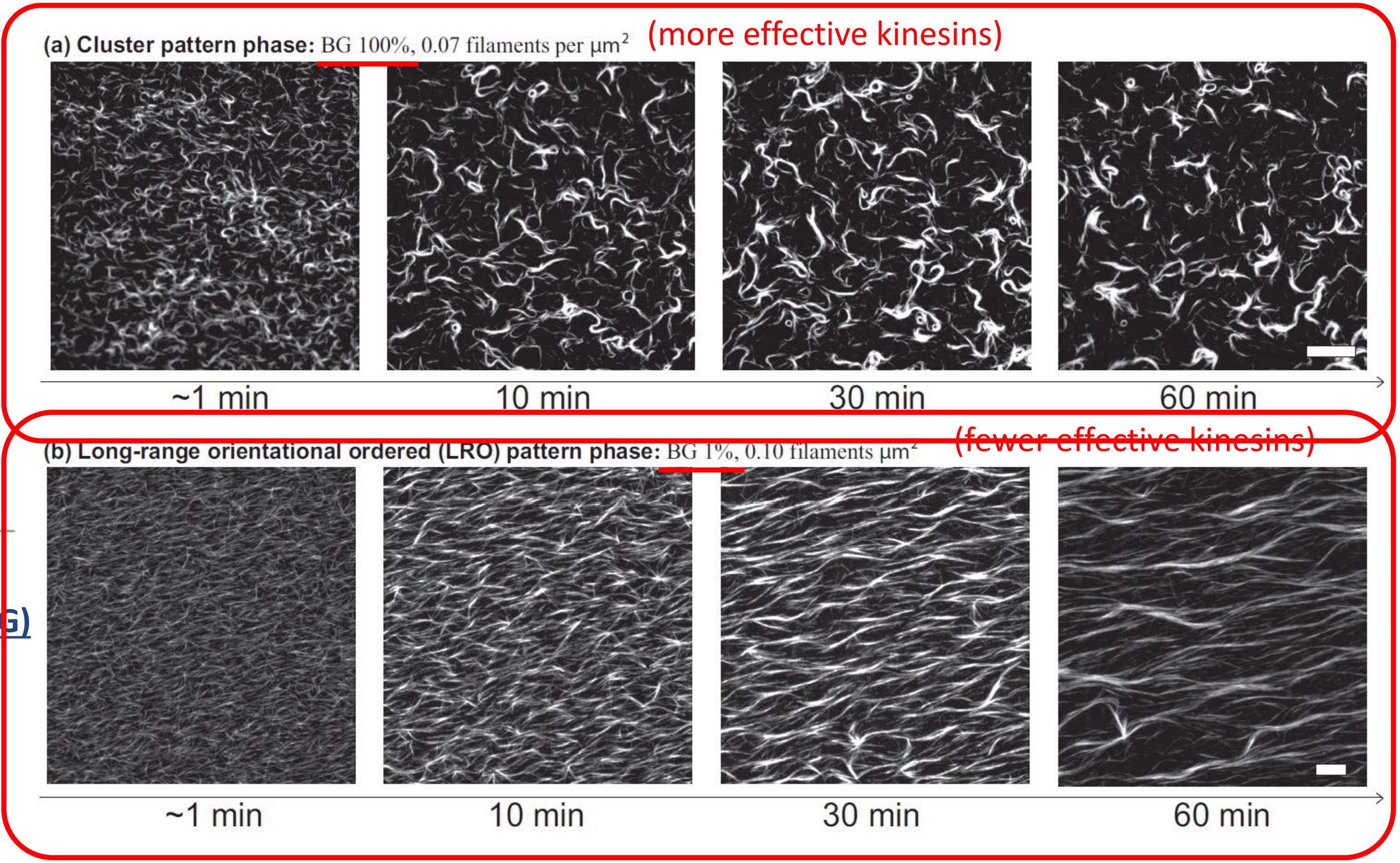


Afroze, Inoue, … , Hiraiwa, …, Kakugo,
BBRC 563, 73 ('21)

What can be control factors of these varieties of collective behavior?

(1) Global ordering or clustering?

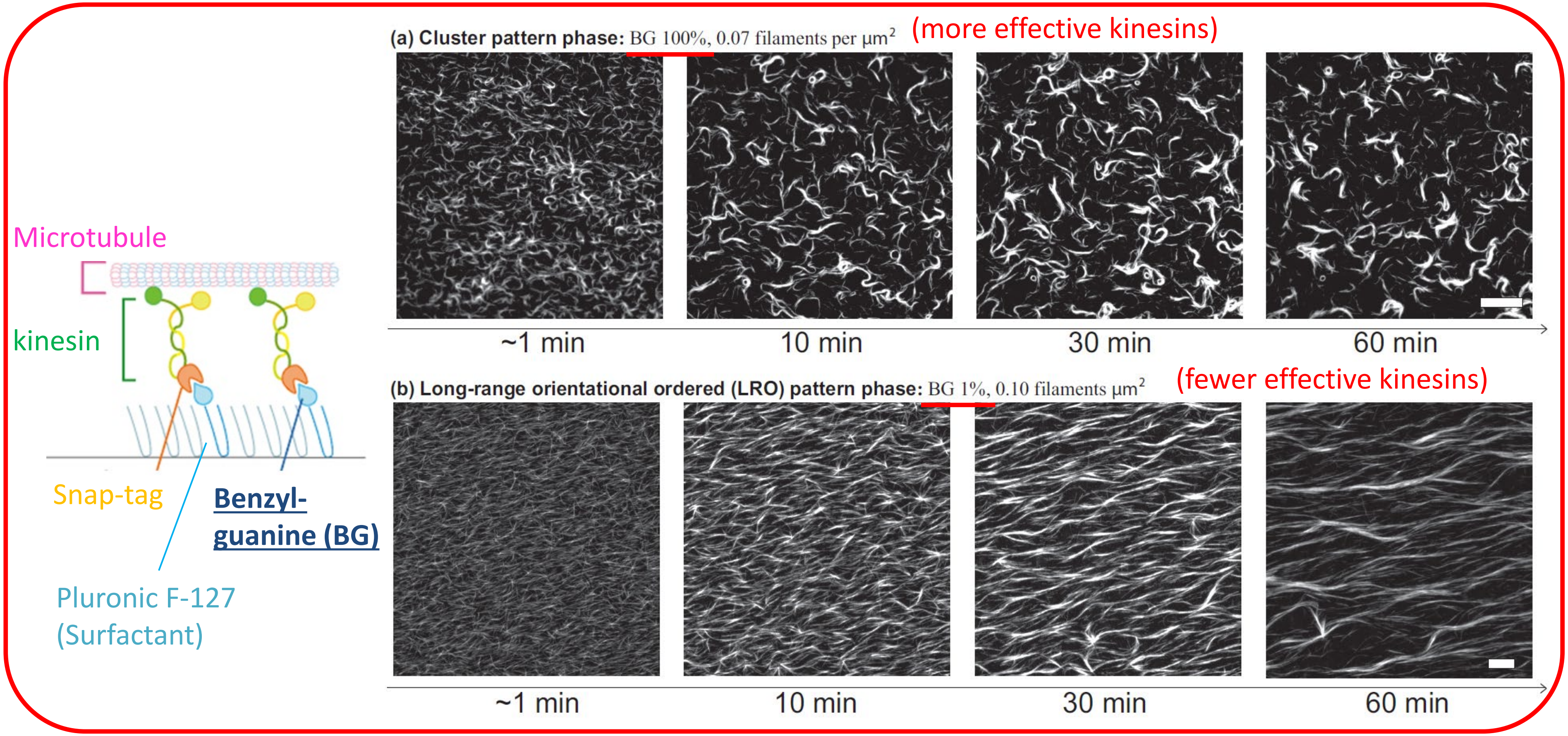




Tanida, ..., Hiraiwa, ..., Sano, *Phys. Rev. E* 101, 032607 (2020)

What controls whether the system shows "global ordering" or "clustering"?

(1) Global ordering or clustering?



Tanida, …, Hiraiwa, …, Sano, *Phys. Rev. E* 101, 032607 (2020)

What controls whether the system shows "global ordering" or "clustering"?

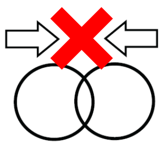
What controls this difference?
- Importance of volume exclusion

Tanida, ..., Hiraiwa, ..., Sano, *Phys. Rev. E* 101, 032607 (2020).

Theory

$$\boldsymbol{\Xi}(\boldsymbol{q}_i)\frac{d}{dt}\boldsymbol{x}_i = v_0\hat{\boldsymbol{q}}_i + \underline{\boldsymbol{K}_i(\{\boldsymbol{x}_j\})}$$

Volume exclusion



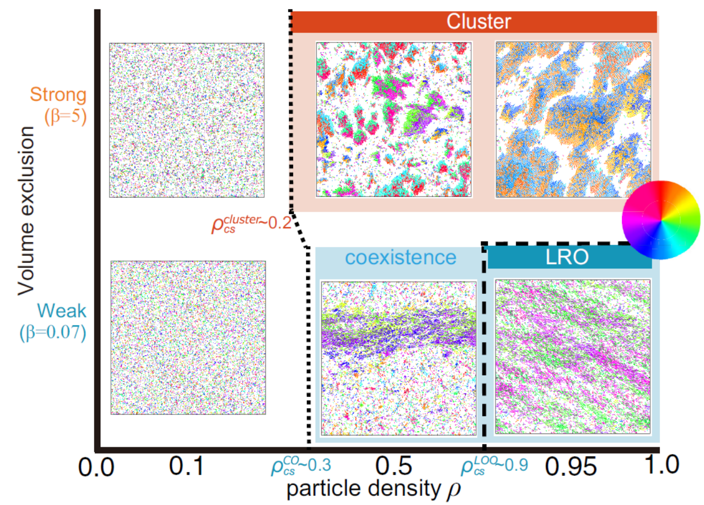
$$\boldsymbol{K}_i(\{\boldsymbol{x}_j\}) = -\beta\sum_{j:\,|\boldsymbol{d}_{ij}|<r}\left[\frac{r\,\boldsymbol{d}_{ij}}{|\boldsymbol{d}_{ij}|^2} - 1.0\right]$$

with $\boldsymbol{d}_{ij} = \boldsymbol{x}_i - \boldsymbol{x}_j$

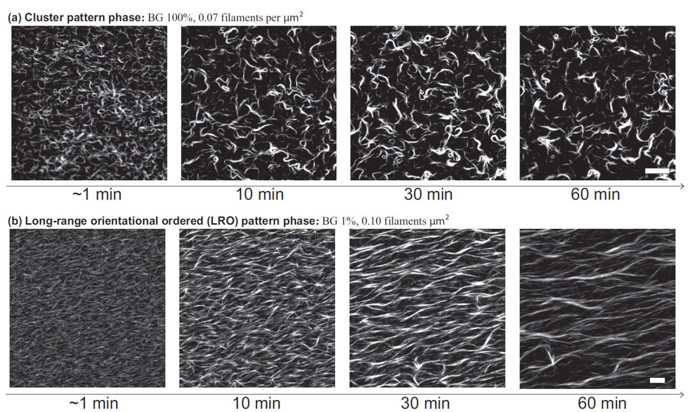
$$\boldsymbol{\Xi}(\boldsymbol{q}_i) = \zeta_\parallel\hat{\boldsymbol{q}}_i\hat{\boldsymbol{q}}_i + \zeta_\perp(1-\hat{\boldsymbol{q}}_i\hat{\boldsymbol{q}}_i) \quad (\zeta_\parallel \ll \zeta_\perp)$$

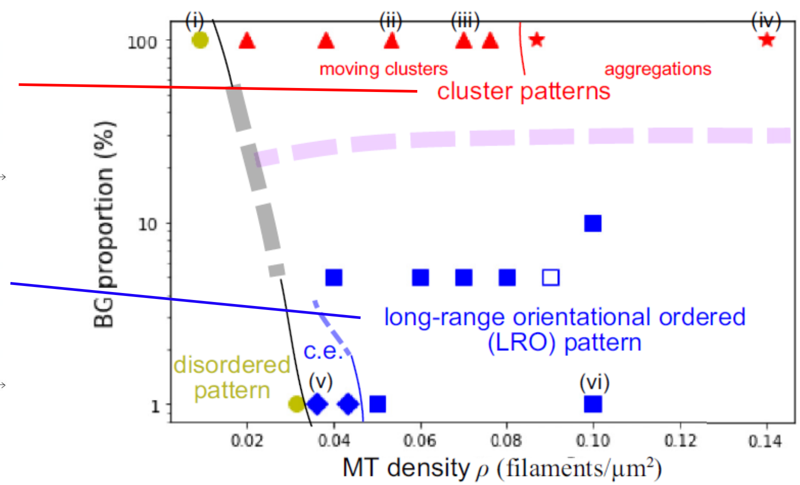
$$\frac{d}{dt}\boldsymbol{q}_i = \underline{\boldsymbol{L}_i} + \boldsymbol{\xi}_i \quad \text{with } |\boldsymbol{q}_i| = 1$$

Bidirectional alignment $\boldsymbol{L}_i = \alpha_{AL}\sum_{j:\,|\boldsymbol{d}_{ij}|<r}(\hat{\boldsymbol{q}}_i\cdot\hat{\boldsymbol{q}}_j)\hat{\boldsymbol{q}}_j$



Exp.

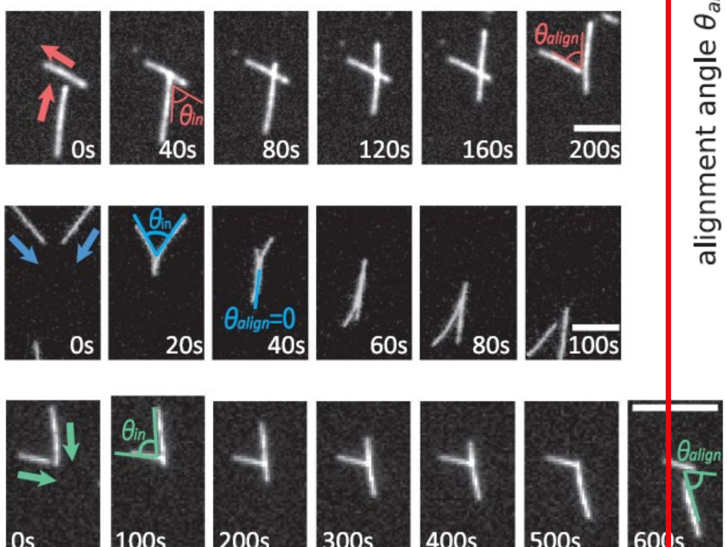


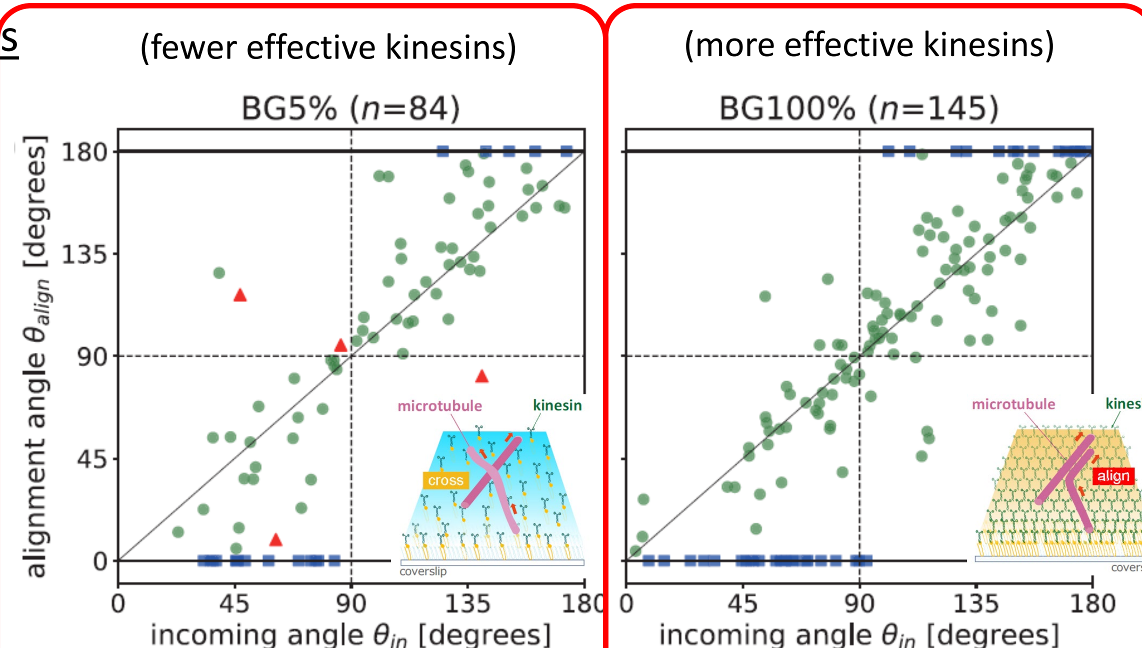


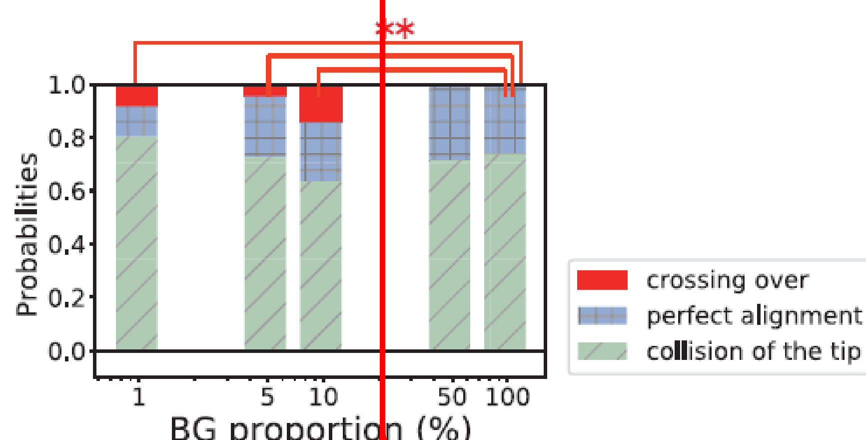
<u>Degree of crossing-over is a control factor</u>

Experimental verification of crossover

Two-microtubule collision statistics



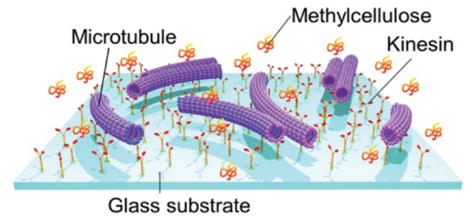




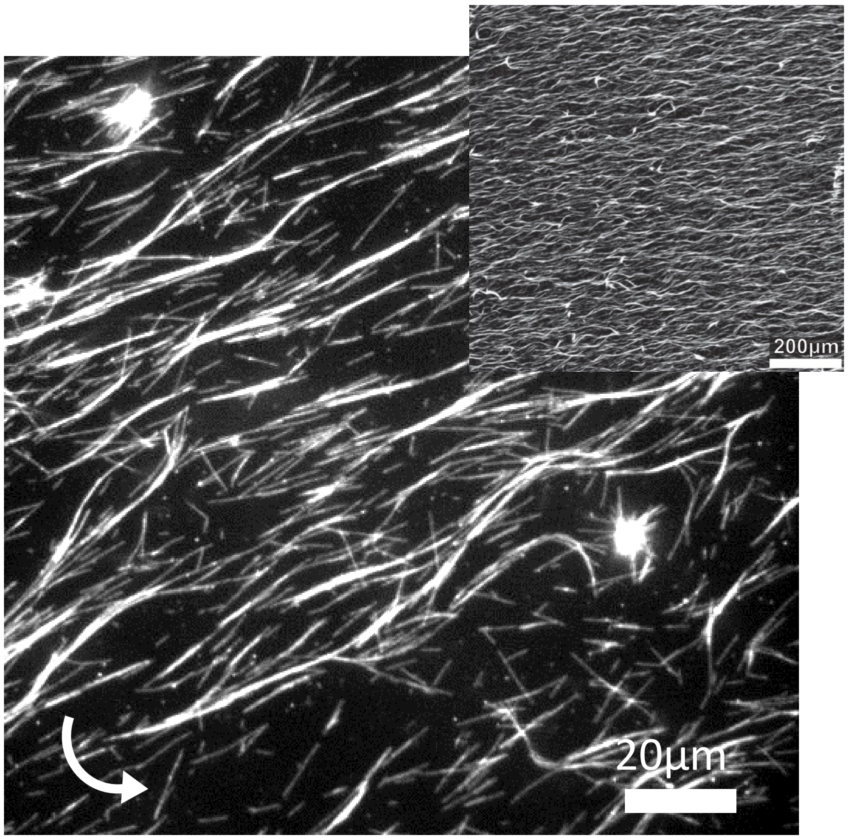
Tanida, …, Hiraiwa, …, Sano,
Phys. Rev. E 101, 032607 (2020).

(2) Chirality effect: Bi-directional orientation rotation or mono-polar flocks?

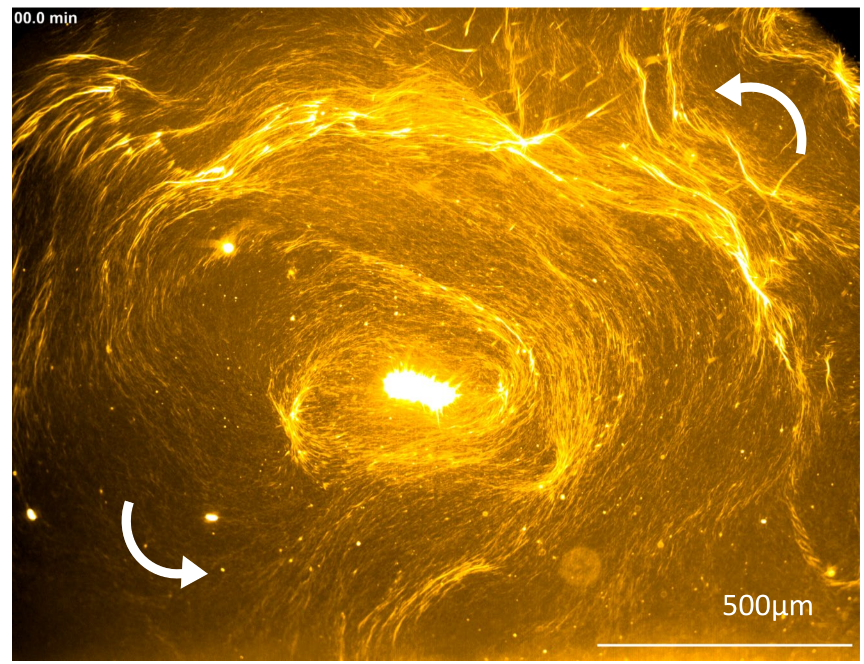
Afroze, … , Hiraiwa, …, BBRC 563, 73 ('21)
Hiraiwa, Akiyama et al. PCCP 24, 28782 ('22)



(Schematic from Inoue et al. Nanoscale 2015)



Tanida, …, Hiraiwa, … Sano, PRE 2020.



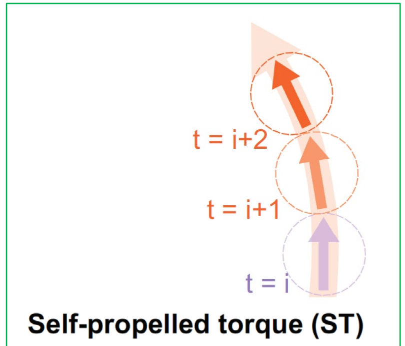
Afroze, Inoue, … , Hiraiwa, …, Kakugo, BBRC 2021.

What is a possible control factor between these two dynamic self-org. patterns?

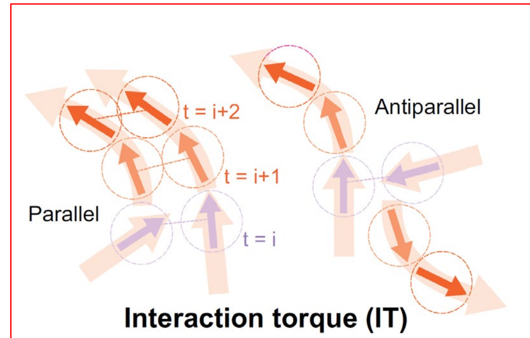
What controls this difference?
- Transition by the balance of two different torques

$$\begin{cases} \boldsymbol{\Xi}(\boldsymbol{q}_i)\dfrac{d}{dt}\boldsymbol{x}_i = v_s\boldsymbol{q}_i + \boldsymbol{K}_i(\{\boldsymbol{x}_j\}) \\ \dfrac{d}{dt}\boldsymbol{q}_i = \boldsymbol{M}_i + \boldsymbol{L}_i + \boldsymbol{\xi}_i \end{cases}$$

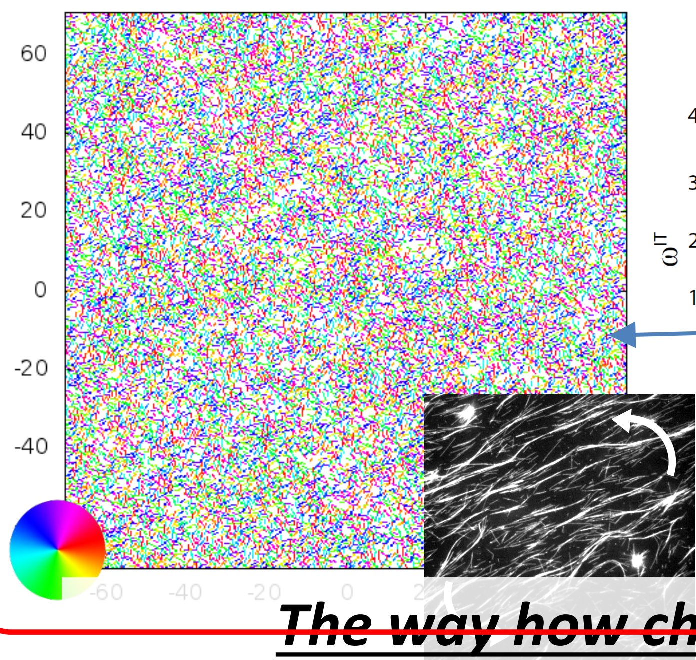
in self part *in interaction part*



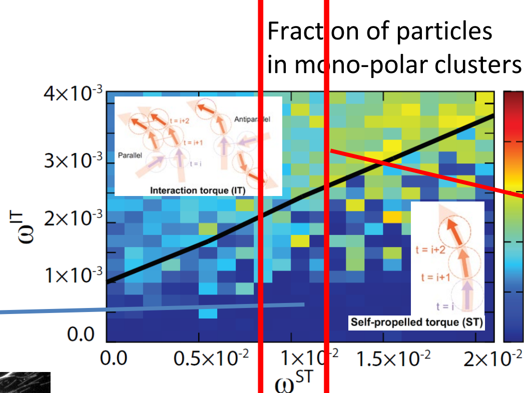
$$\boldsymbol{M}_i = \omega_{ST}(\hat{\boldsymbol{z}} \times \boldsymbol{q}_i)$$



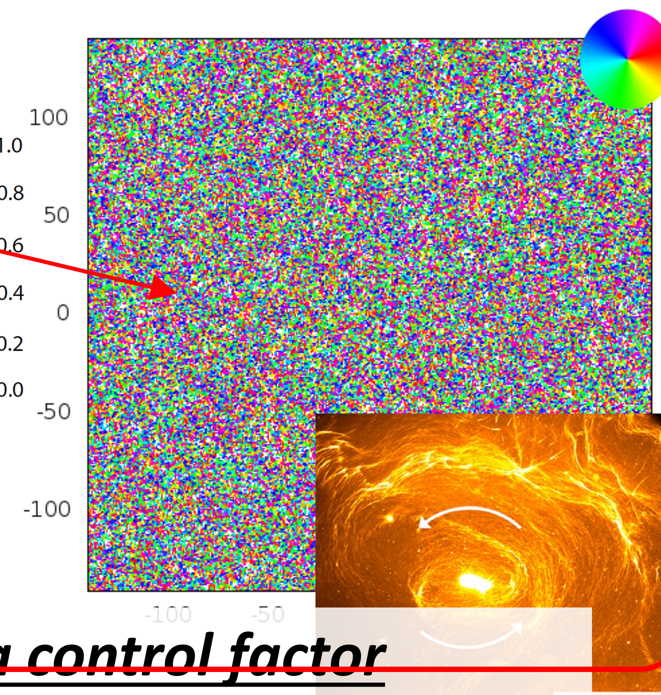
$$\boldsymbol{L}_i = \left(\omega_{IT}\sum_{j:\,|\boldsymbol{x}_i-\boldsymbol{x}_j|<r}^{(j\neq i)} 1\right)(\hat{\boldsymbol{z}} \times \boldsymbol{q}_i)$$



Tanida, ..., Hiraiwa, ..., PRE (2020).



Hiraiwa, Akiyama, et al.
PCCP (2022)

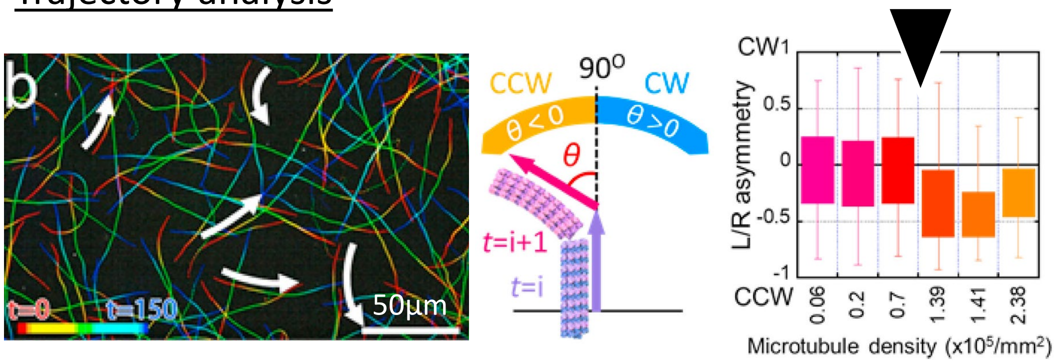


Afroze, Inoue, et al. BBRC (2021)

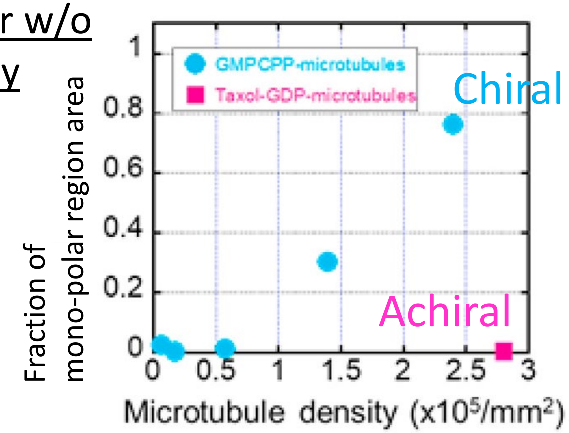
<u>The way how chirality appears is a control factor</u>

Experimental verifications of interaction torque

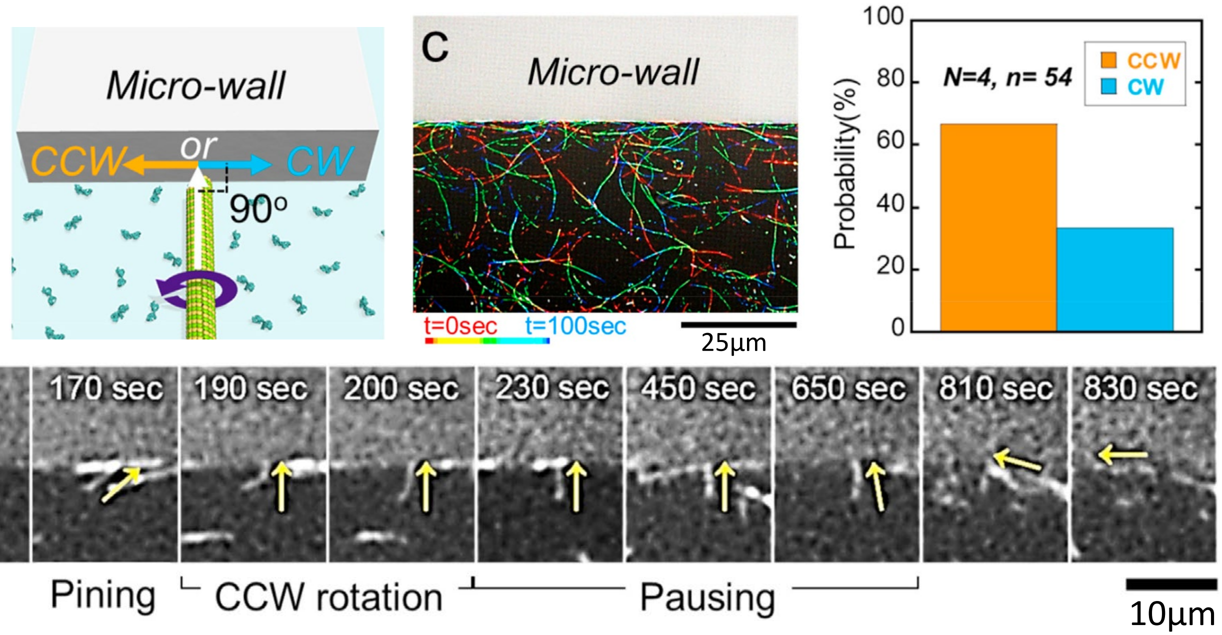
Trajectory analysis



With or w/o chirality



Wall collision analysis



Afroze, Inoue, …, Hiraiwa, …, Kakugo, BBRC 563, 73 (2021)

Brief summary of this part

- Various patterns of dynamic self-organization of gliding biofilaments can be explained by the same framework introduced to simulate cell collectives

- Newly identified factors controlling patterns;
(1) volume exclusion
(2) type of torque (chirality) – ST or IT

Tanida, …, Hiraiwa, …, Sano (2020): Phys. Rev. E

Afroze, …, Hiraiwa, …, Kakugo (2021): Biochem. Biophys. Res. Commun.

Hiraiwa, Akiyama, …, Kakugo (2022): Phys. Chem. Chem. Phys.

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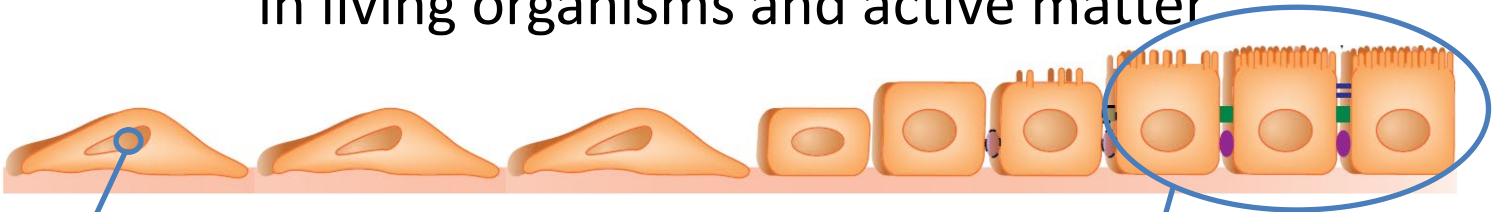
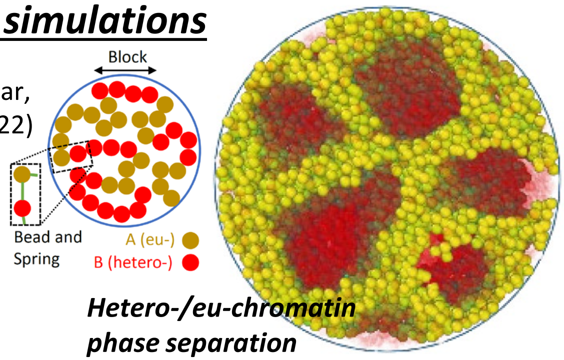
Theoretical studies on (dynamic) self-organization in living organisms and active matter



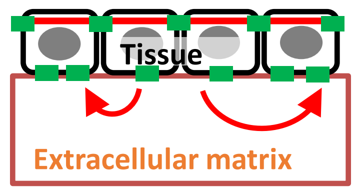
<u>Chromatin organization and dynamics; based on polymer-physics simulations</u>

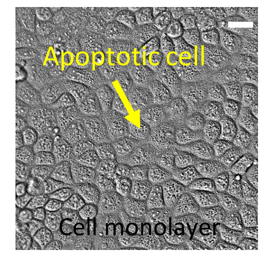
Das, Sakaue, Shivashankar, Prost, **Hiraiwa,** *eLife* (2022)

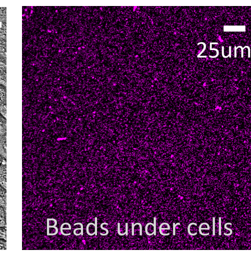


<u>Tissue morphogenesis and homeostasis; with continuum-mechanics theory</u>

Lou, Kawaue, Yow, Toyama, Prost, **Hiraiwa**, *Biomech. Model. Mechanobiol.* (2022).



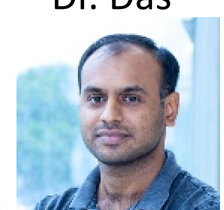




Hiraiwa-lab personnel	2 Postdocs (Dr. Lou, Dr. Das; appearing as first authors above) @Mechanobiology Institute, National University of Singapore (- March 2023) 1 Postdoc, 1 PhD Student @IOP, AS (April 2023 -)

Dr. Lou

Dr. Das

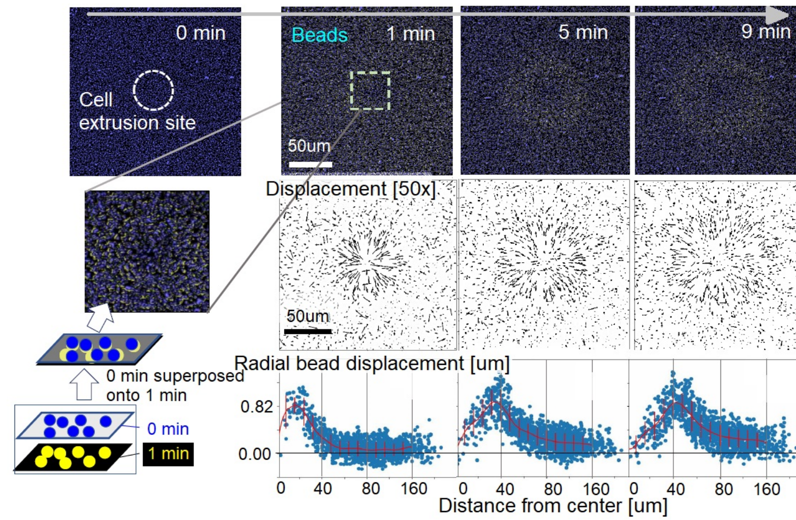


Top figure: Adapted from : https://www.mechanobio.info/development/what-is-the-epithelial-to-mesenchymal-transition-emt/

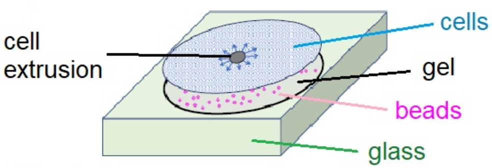
Long-range force propagation in a weakly adhesive substrate generated by a tissue

***Lou**, Kawaue, Yow, Toyama, Prost, **Hiraiwa** (2022) Biomech. Model. Mechbiol.*
"Interfacial friction and substrate deformation mediate long-range signal propagation in tissues"

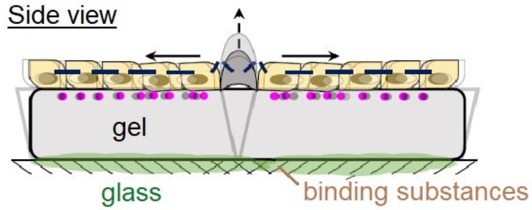
Quantitative analysis

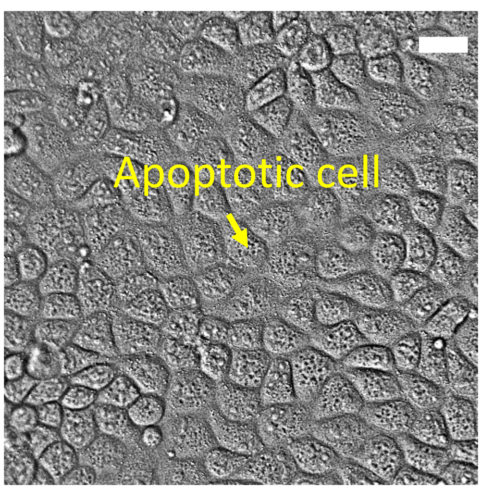


Top view

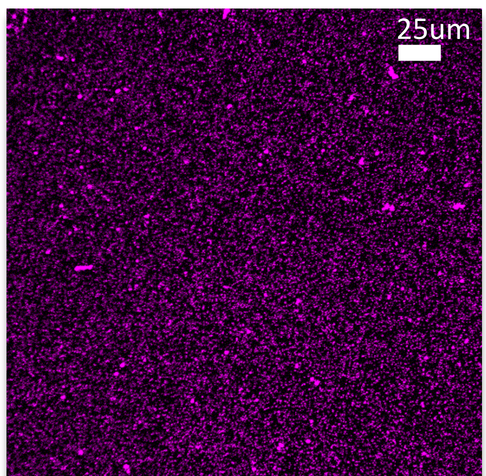


Side view





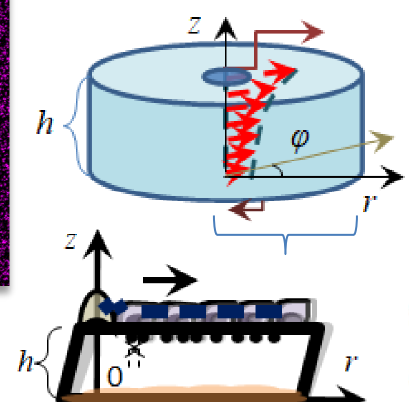
MDCK, Duration=11 min

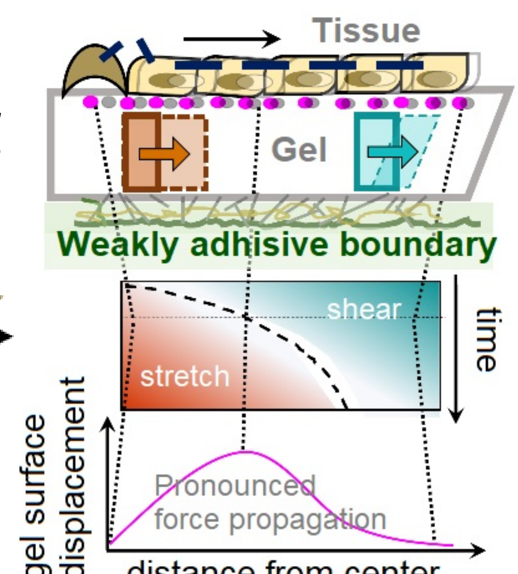


"Traction microscopy" obs.

Experimental data provided by Toyama-lab (MBI, NUS);
esp. Ivan Yow, Dr. Takumi Kawaue.

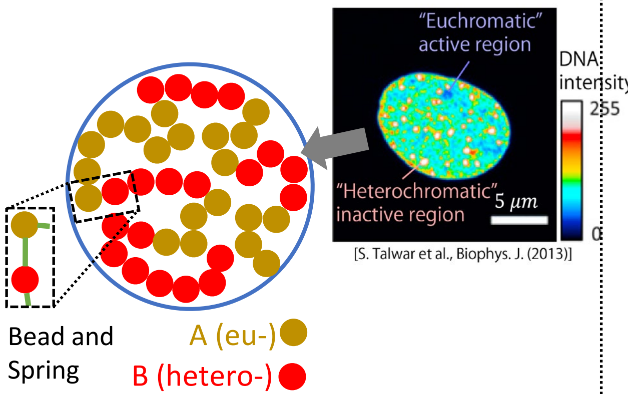
Elasticity theory for substrate gel

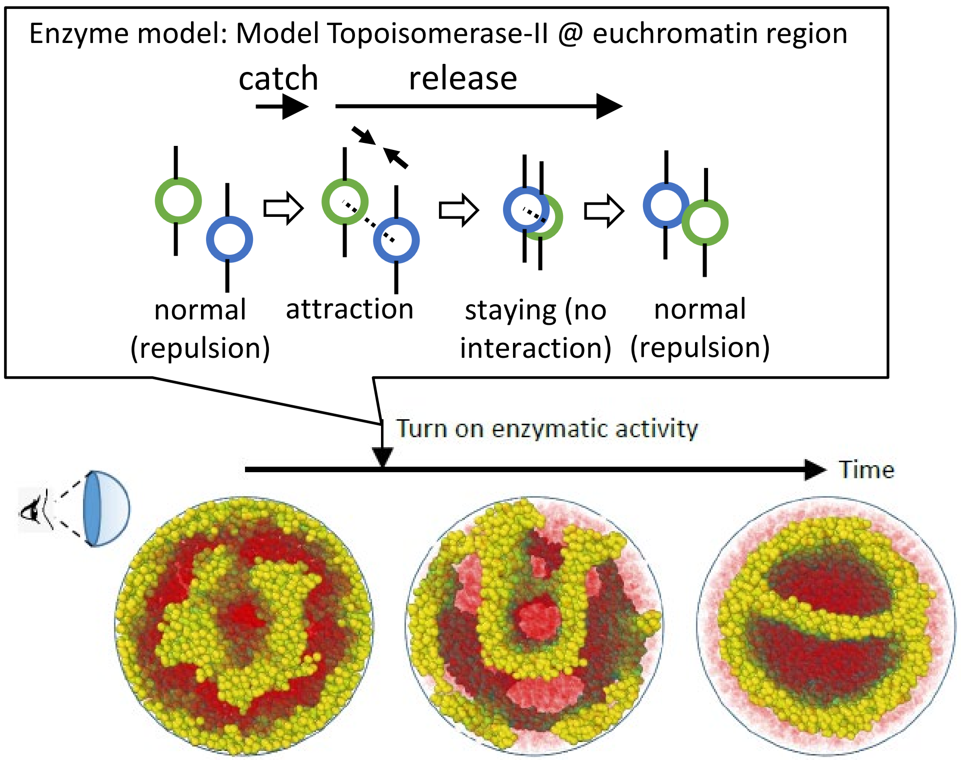


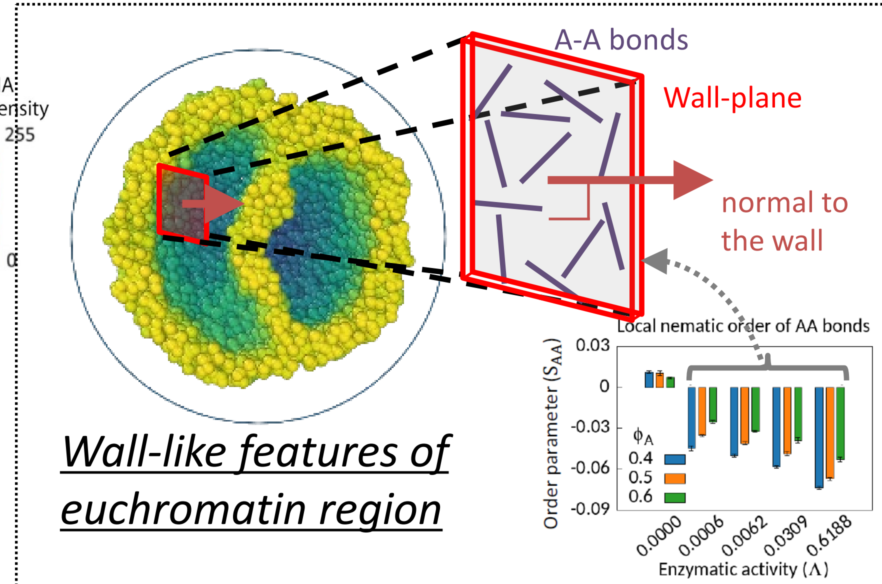


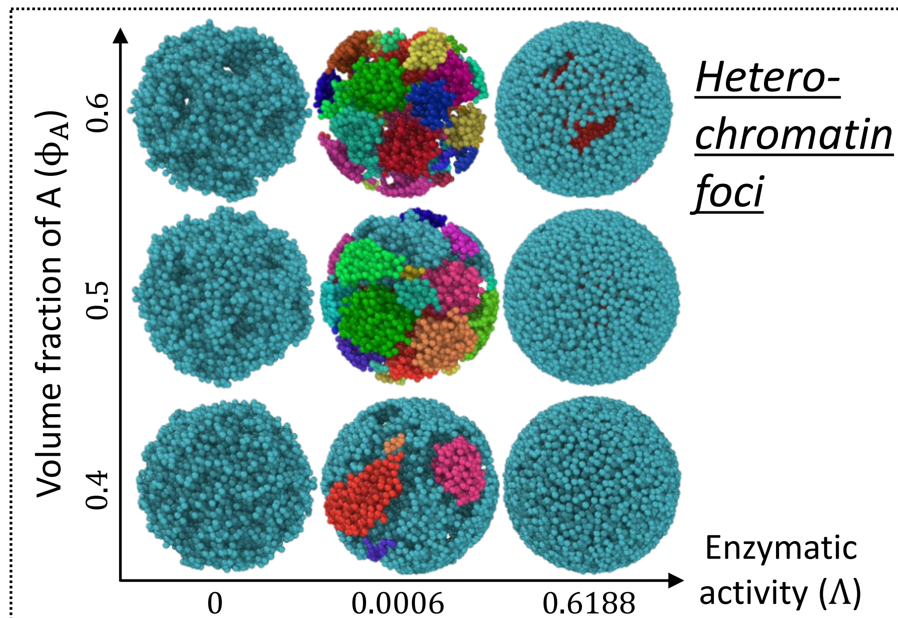
Mechanical influence of enzymatic activity to chromatin organization

***Das**, Sakaue, Shivashankar, Prost, **Hiraiwa** (2022) eLife, "How enzymatic activity is involved in chromatin organization"*









Future Plan:

Toward living organisms further – Integrating dynamic self-organization study and biomechanics

1. Multi-Cellular Scale … <u>Cellular DSO with fragile epithelial integrity</u>

- extend our study of cellular dynamic self-organization (DSO) of migrating cells to the situations when the tissue can experience fracture, change tissue topology or cells can depart from the tissue

2. Multi-Molecular Scale … <u>Active viscoelastic phase separation</u>

- study theoretically how mechanical perturbations of extra-molecules in action, like enzymes, affect the viscoelastic phase-separation in a living cell.

Future plan besides research

To launch the biophysicist beyond-lab activity

Plan: Online communication platform + Regular joint-lab meetings

- ✓ Platform – We already started communication by LINE group
- ✓ Regular meeting – Not yet. The details are under consideration.

> Goal (Personal desire) … To reach at **new research ideas** which can arise only through collections of expertise of different people

Who agreed and joined our LINE group so far:

- ➢ Guo-Chin Lin (Exp; Assoc. RF at IOP)
- ➢ Hong-yan Shih (Theory; Assist. RF at IOP)
- ➢ Keita Kamino (Exp; Assist. RF at IMB)
- ➢ Wei-Hsiang Lin (Exp; Assist. RF at IMB)
- ➢ Myself (Theory; Assoc. RF at IOP)
- ➢… More labs welcome!

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Group website: https://theorphysbiolgroup.wixsite.com/oursite

Dynamic self-organization in living organisms and active matter

Before April 2023

MBI MECHANOBIOLOGY INSTITUTE
National University of Singapore

After April 2023

INSTITUTE OF PHYSICS ACADEMIA SINICA

ACADEMIA SINICA

Five Representative works for 5 years:

1. 2020 Dynamic Self-Organization of Idealized Migrating Cells by Contact Communication
2. 2022 Dynamic self-organization of migrating cells under constraints by spatial confinement and epithelial integrity
3. 2022 Interfacial friction and substrate deformation mediate long-range signal propagation in tissues
4. 2022 How enzymatic activity is involved in chromatin organization
5. 2022 Collision-induced torque mediates transition of chiral dynamic patterns formed by active particles

Future plans:

1. Cellular DSO with fragile epithelial integrity
2. Active viscoelastic phase separation
3. etc