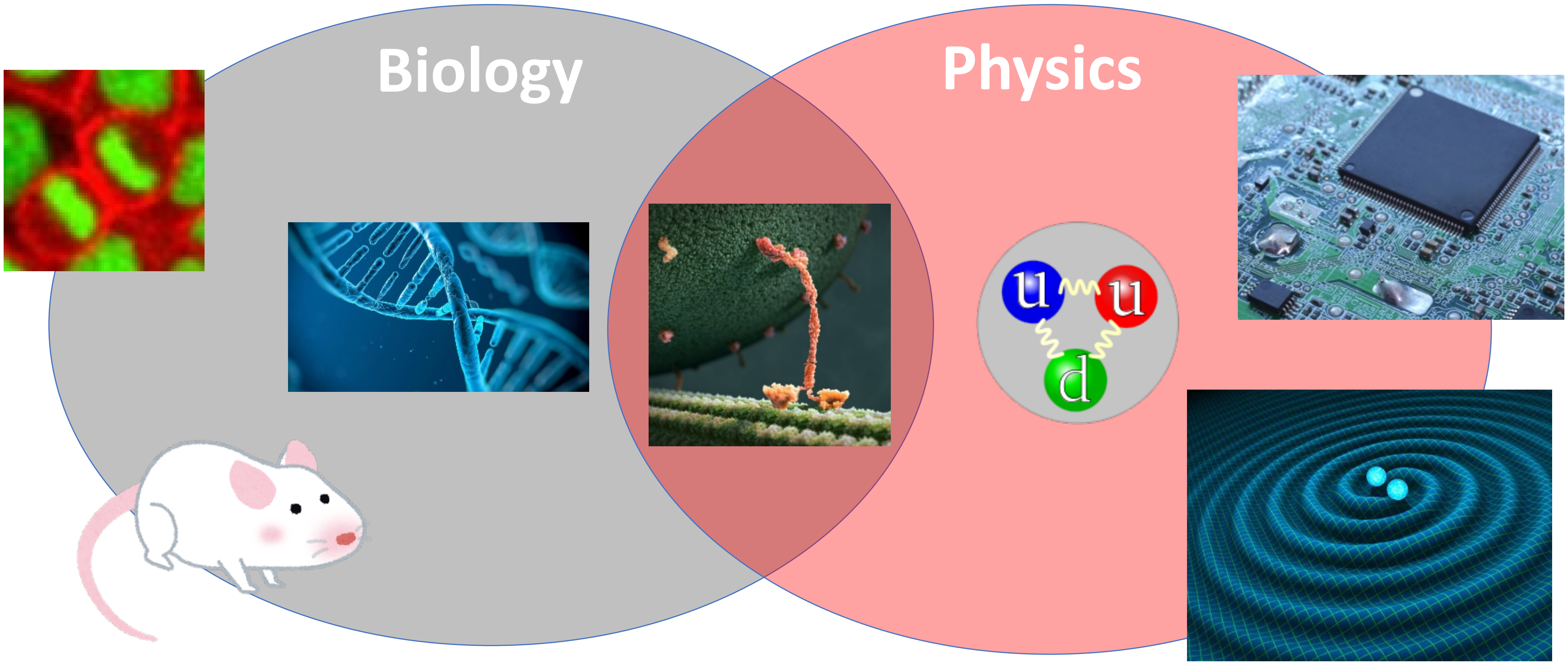
Nonequilibrium physics in multicellular systems

川口喬吾
Kyogo Kawaguchi
Riken BDR (from Sep 2018)


Biology
Physics
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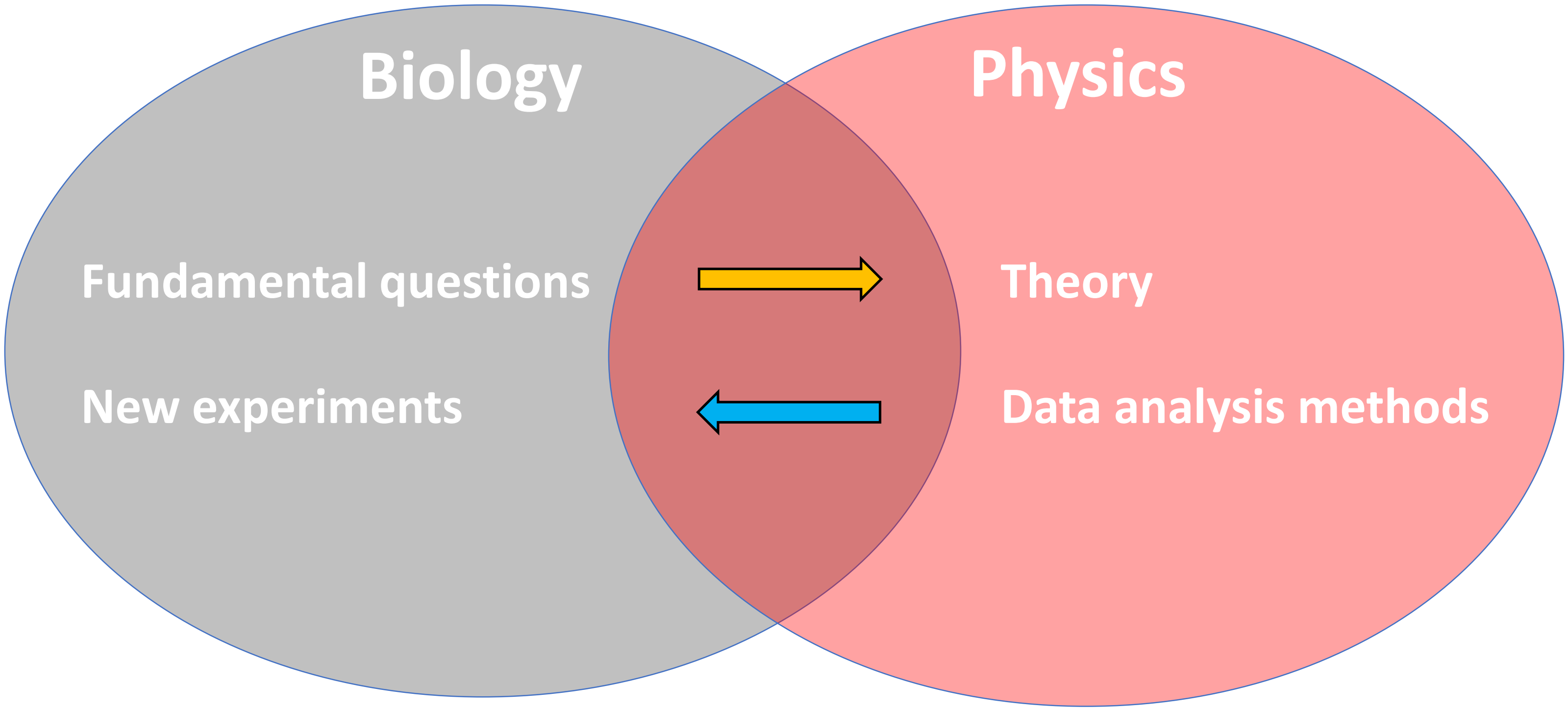

Biology
Physics
Fundamental questions
New experiments
Theory
Data analysis methods

Outline

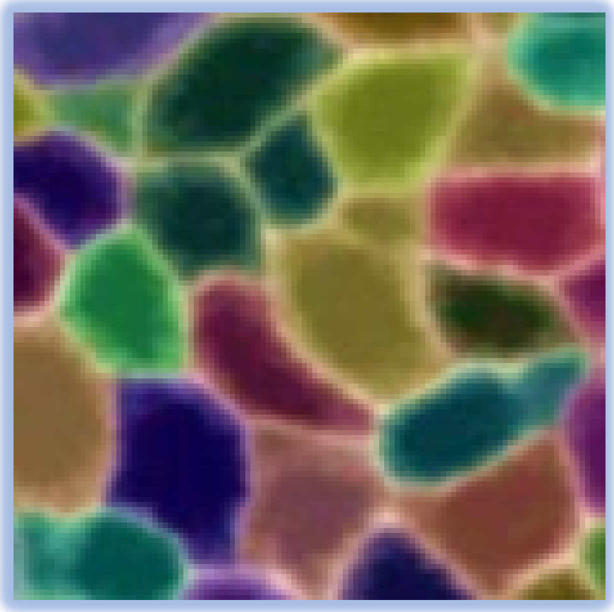
1. Skin (tissue) homeostasis
   Interacting particle system

2. Collective motion in cultured neural stem cells
   Active nematics

3. Acknowledgements

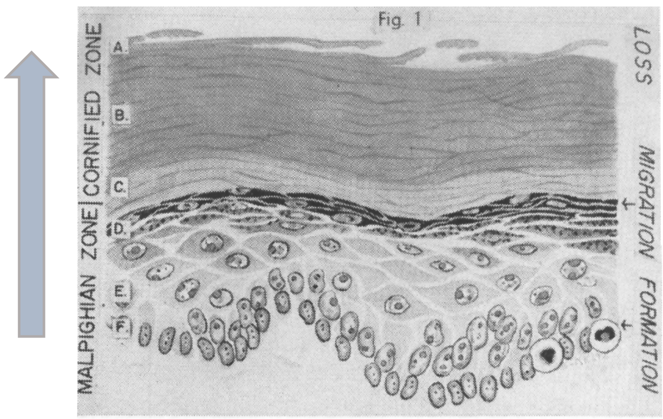
1. Skin homeostasis is maintained by nearest neighbor fate coupling

[Science 352, 1471 (2016), Phys Rev E 96 012401 (2017), Cell Stem Cell 23, 677 (2018)]



Tissue homeostasis:
Epidermal stem cells
are confined in a two-dimensional layer

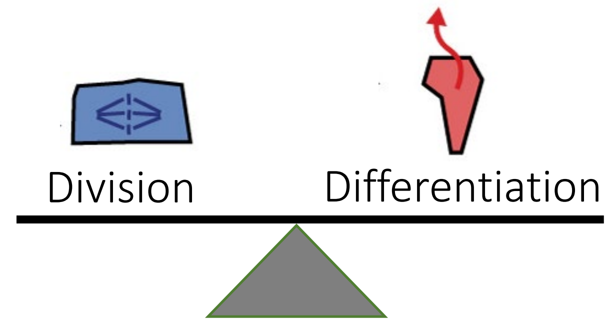
Cross section

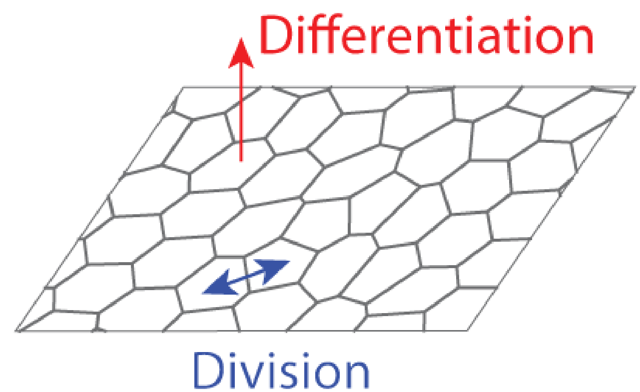


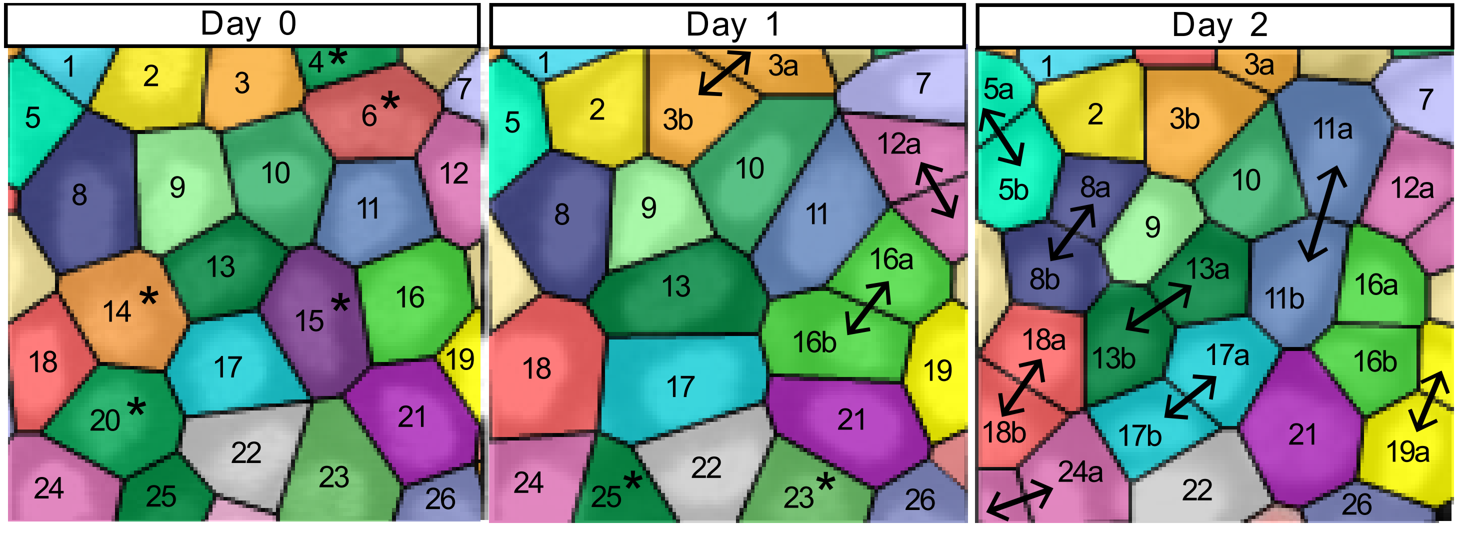
→ Basal layer = stem cells
(基底細胞層)

Leblond, Walker (1956)

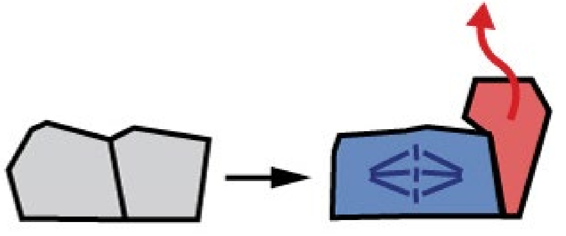
Turn over: 2-10 days



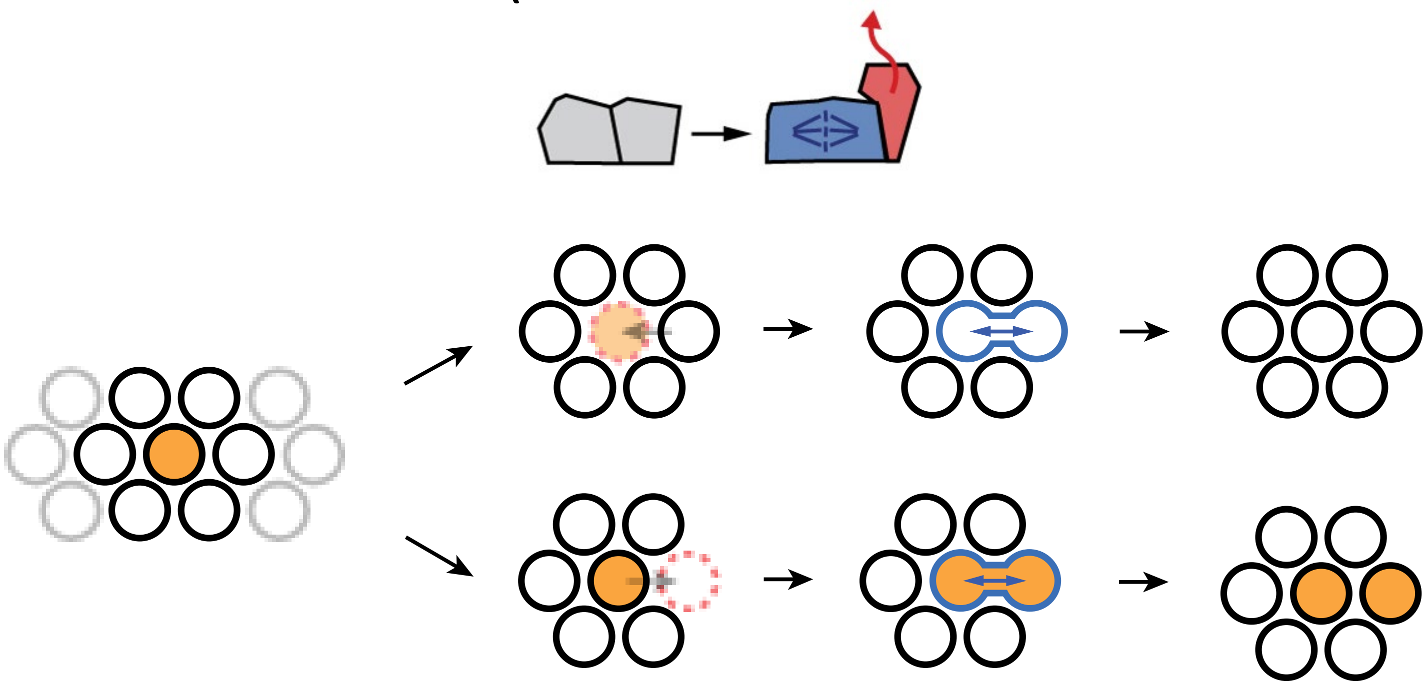


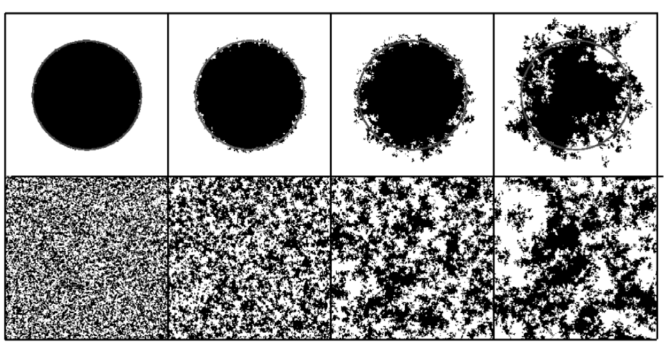


Neighbor fate coupling?



Neighbor fate coupling model = Voter model (DP2)



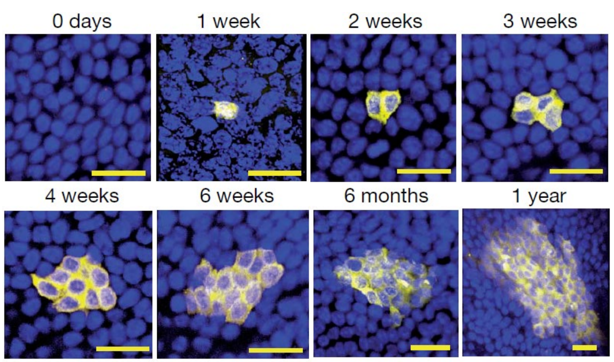


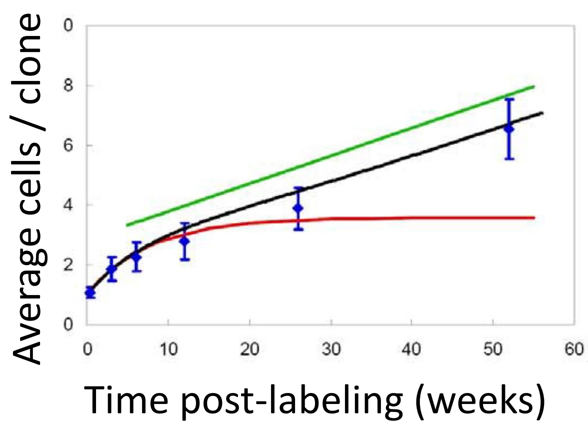
- Model for “voters”
- and critical coarsening
- Universality class (two absorbing states)

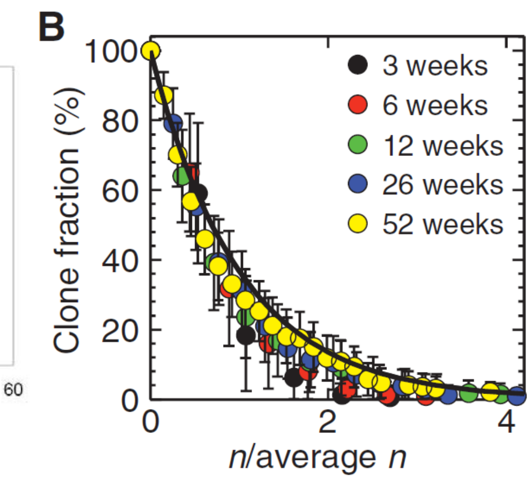
Dornic et al. Phys. Rev. Lett. 87, 045701 (2001)
Hammal et al. Phys. Rev. Lett 94, 230601 (2005)

~10 years ago:
clonal analysis showed scaling behavior

Single cell labeling in live mice (Cre-induced)







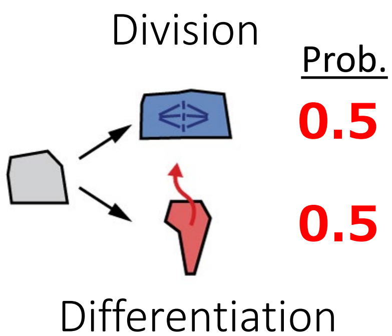
Clayton et al., Nature (2007)
Doupe et al., Dev. Cell (2010)
Klein & Simons, Development (2011)

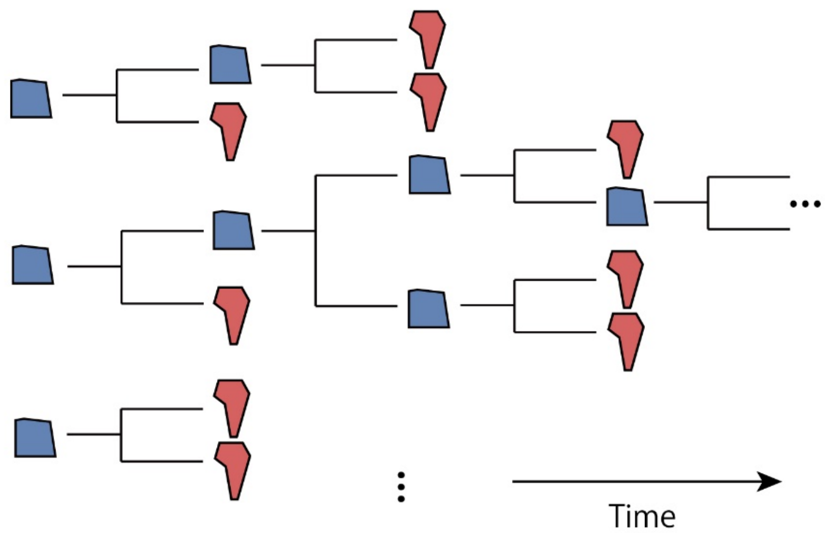
Average number of cells in surviving clones $\langle n(t) \rangle_{n>0} \propto t$

Clone size distribution: $P(\tilde{n}) = \exp[-\tilde{n}]$

$\tilde{n} := n_t / \langle n_t \rangle_{n>0}$

Critical birth death model explains scaling





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Clone size distribution: $P(\tilde{n}) = \exp[-\tilde{n}]$

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Athreya and Ney "Branching Processes" (Dover)
Review: Klein & Simons, Development (2011)

Summary of scaling: experiment and theory

	Experiment (skin)	Cell autonomous Fate (Critical birth death)	Coordinated fate (voter model) d = 1	d = 2	d > 2
Average clone size:	t	t	$t^{1/2}$	$t/\ln t$	t
Clone size cumulative distribution:	e^{-x}	e^{-x}	$e^{-\pi x^2/4}$	e^{-x}	e^{-x}

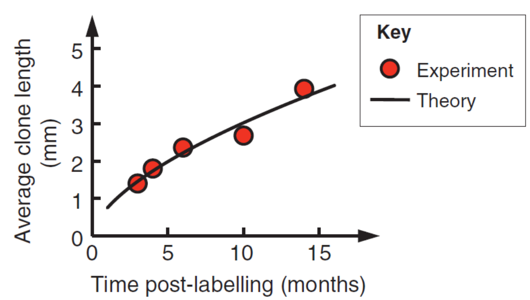
Experiment:

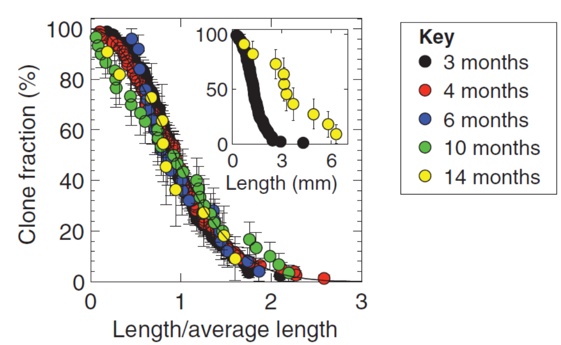
Intestine

[Lopez-Garcia et al. (2010)
Snippert et al. (2010)]

Seminiferous tubule

[Klein et al., (2010)
Yoshida lab]

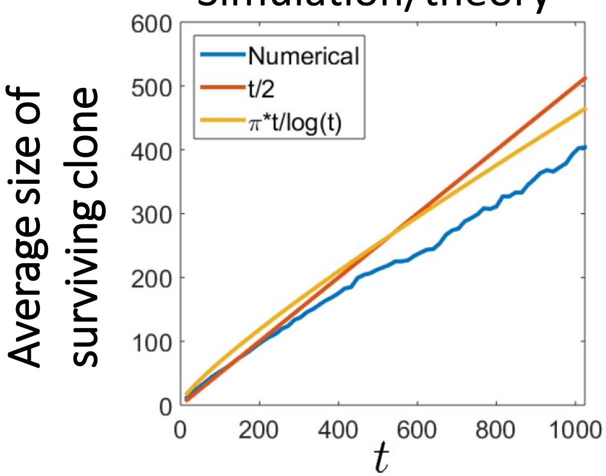




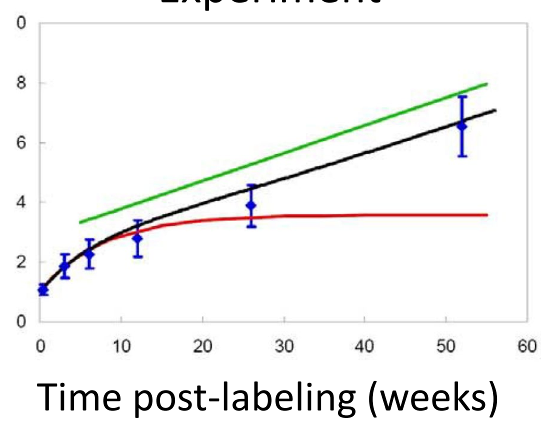
Problem of 2D

	Experiment (skin)	Cell autonomous Fate (Critical birth death)	Coordinated fate (voter model) d = 1	d = 2	d > 2
Average clone size:	t	t	$t^{1/2}$	$t/\ln t$	t
Clone size cumulative distribution:	e^{-x}	e^{-x}	$e^{-\pi x^2/4}$	e^{-x}	e^{-x}

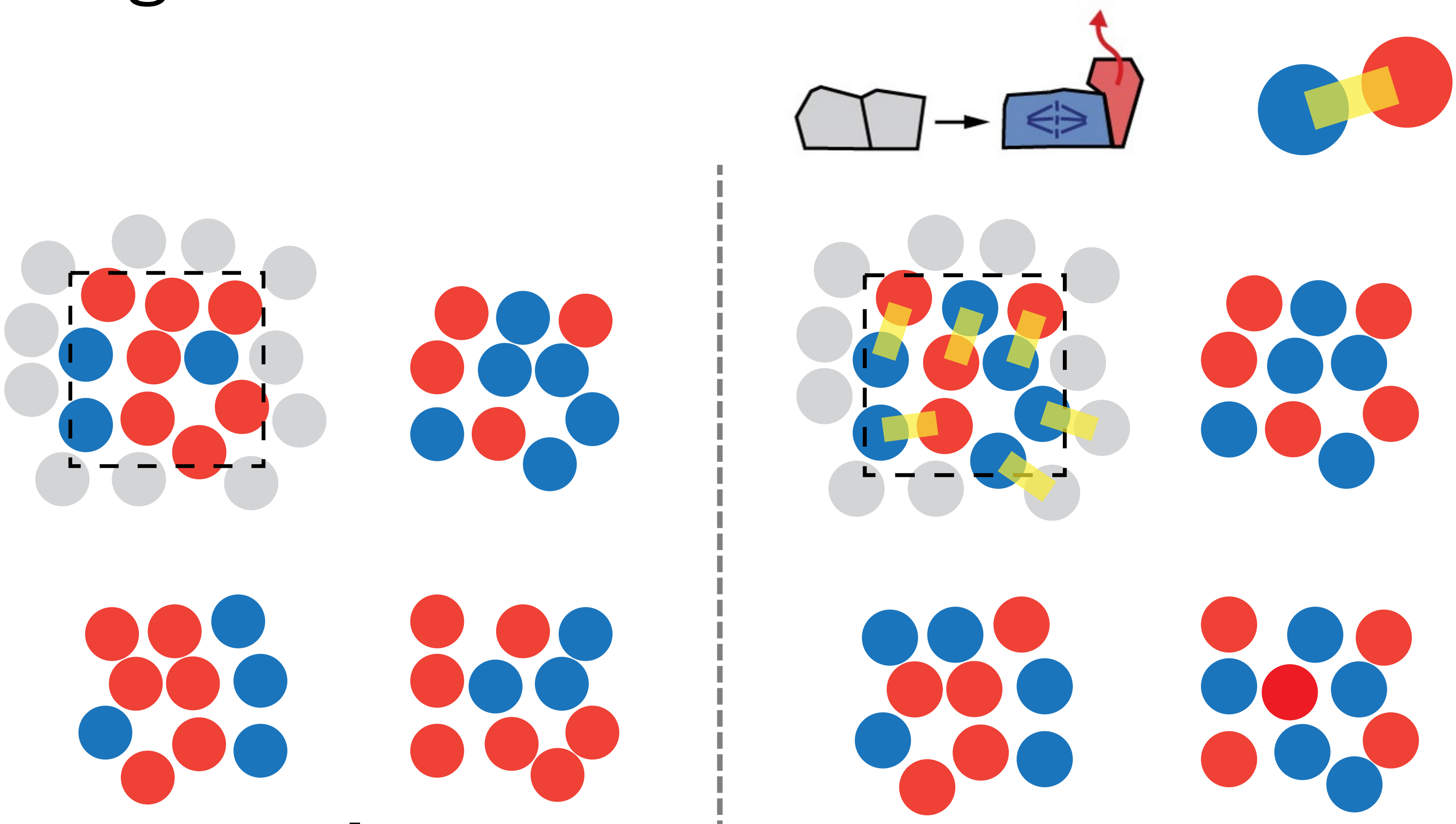
Simulation/theory



Experiment



Fate coordination can be quantified using “fluctuation test”



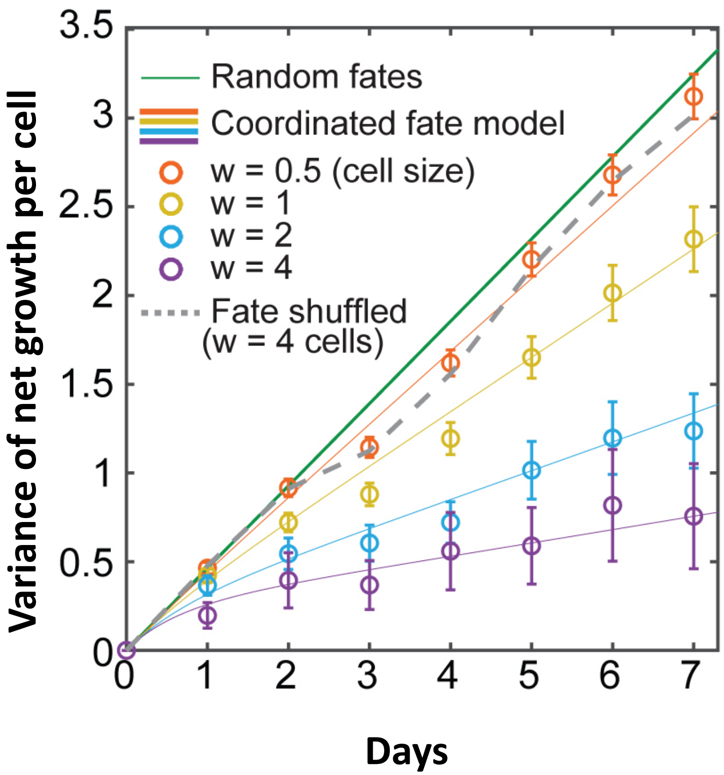
$\sim N^{1/2}$

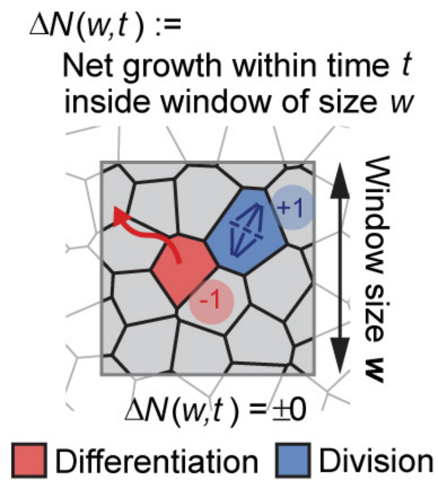
Blue – **Red** = 0 $\boxed{\pm 1.5 \text{ (s.d.)}}$

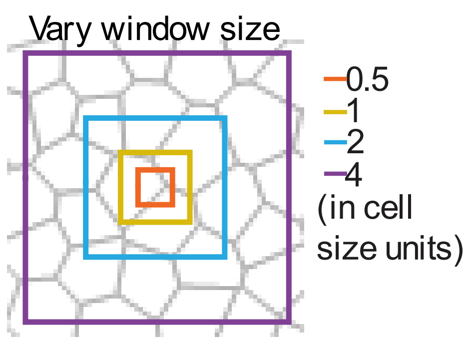
$\sim N^{1/4}$

Blue – **Red** = 0 $\boxed{\pm 0.5 \text{ (s.d.)}}$

Data shows that fates of neighboring cells are coordinated







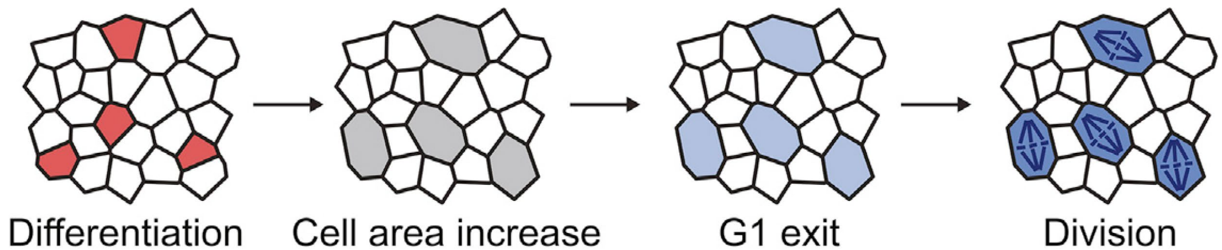
Time scale of coordination: **1-2 days**

Length scale of coordination:
size of a single cell

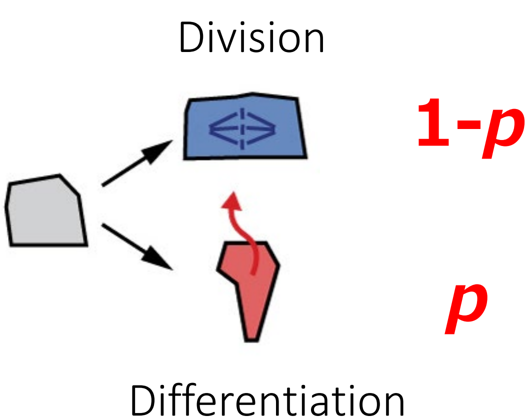
Modeling neighboring fate coupling by local density feedback

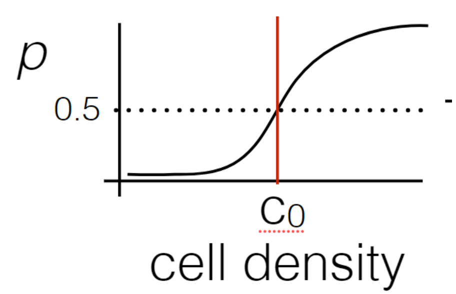
Cell Stem Cell 23, 677 (2018)

From more data analysis:



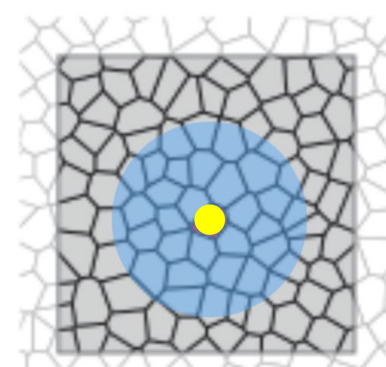
Making model:



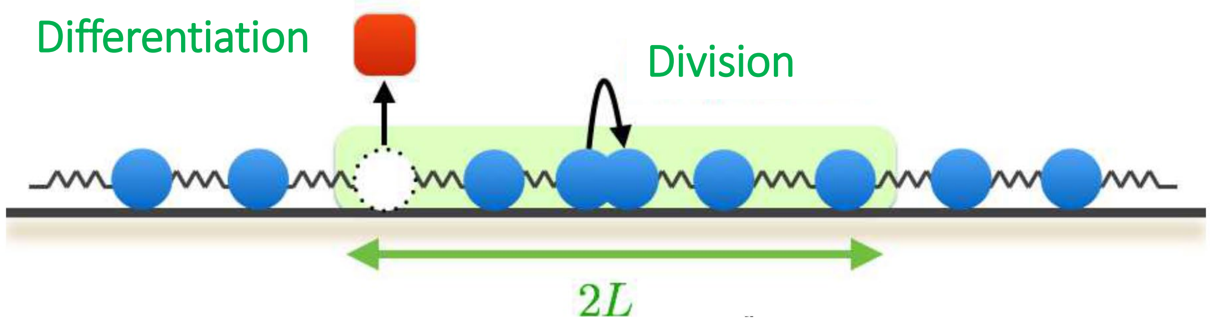


Cell density =

$$\left\langle \frac{\#\ \text{cells}}{\text{region sensed}} \right\rangle_{t\ avg.}$$



Modeling neighboring fate coupling by local density feedback



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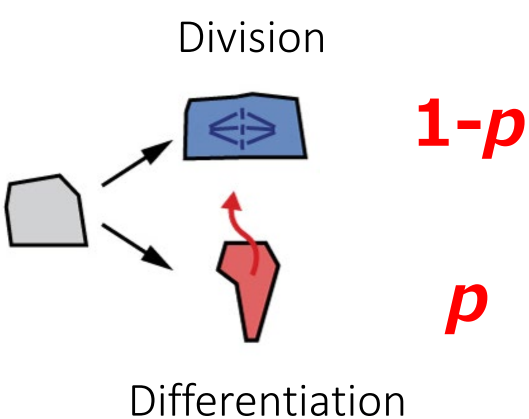

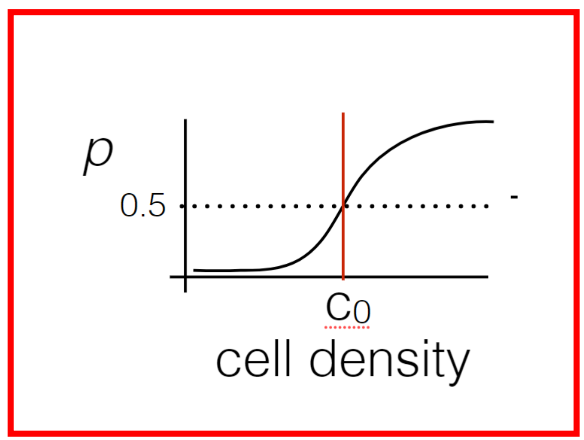

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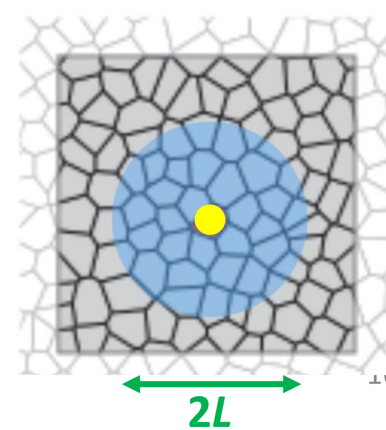
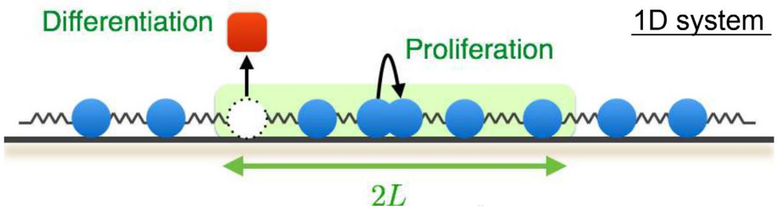


Deriving the voter model action from particle dynamics



Many-body Langevin equation:

-> Continuum dynamics of labeled cell density $\varphi(\vec{x};t)$

-> **MSRDJ** field theory

-> linearize (around uniform density) -> lots of Gaussian integrals

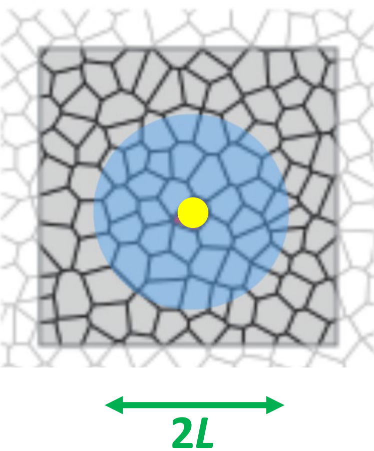
-> renormalization

-> Voter model action (+ irrelevant terms)

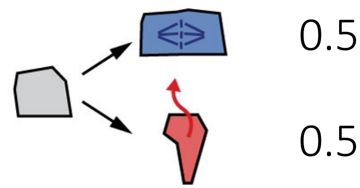
-> Dynamics: $\partial_t \varphi = D\nabla^2\varphi + \sqrt{\varphi(1-\varphi)}\xi$

Yamaguchi and Kawaguchi, in preparation

Model has two regimes separated at the interaction length scale

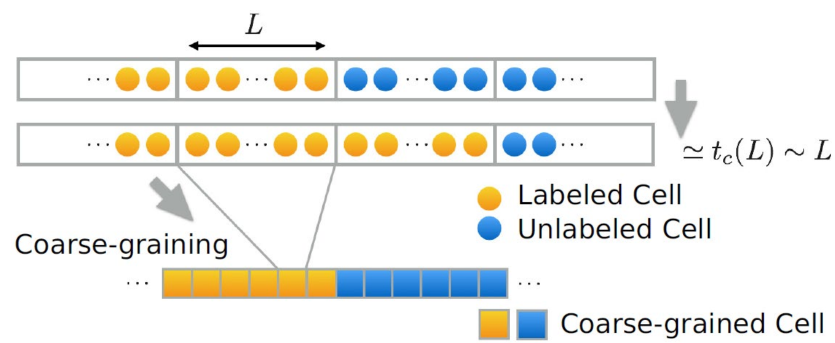


- Small scale regime:
  <u>critical birth death model</u> (cell autonomous)

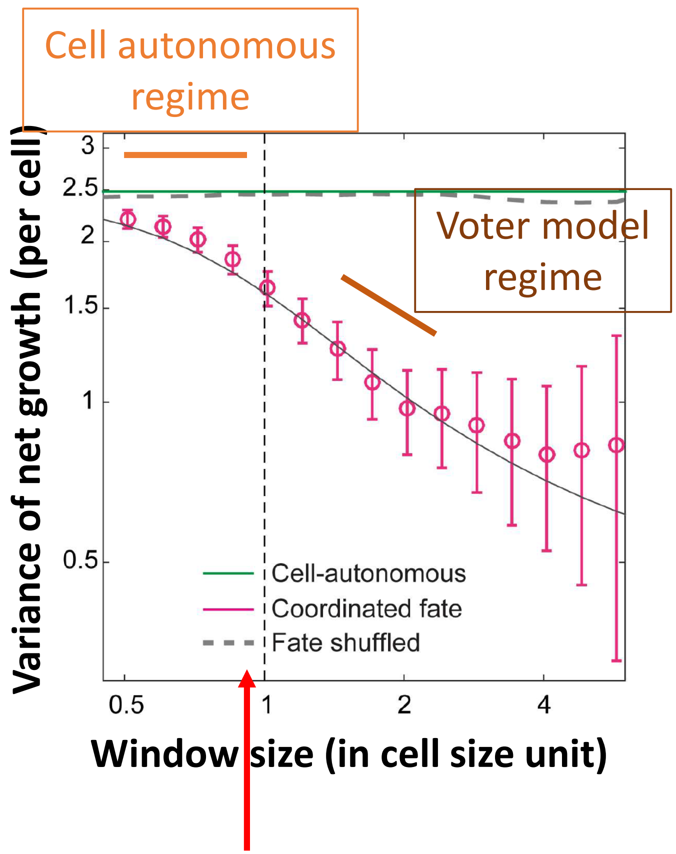


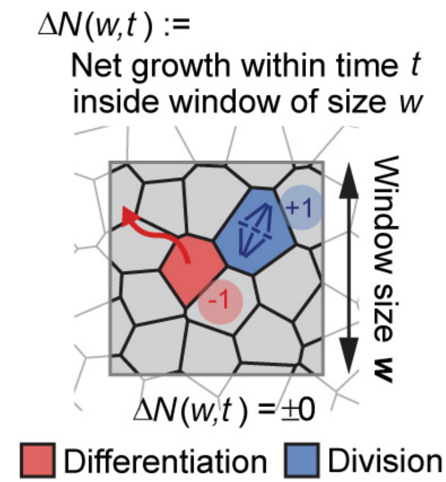
Crossover at ***L***

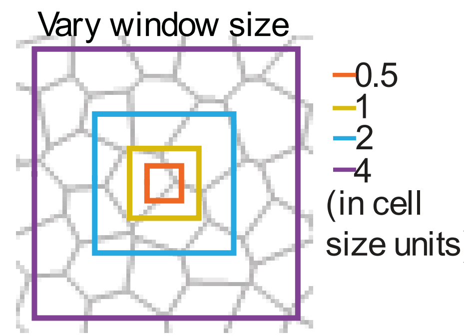
- Large scale regime:
  <u>voter model</u>



Crossover observed in skin data

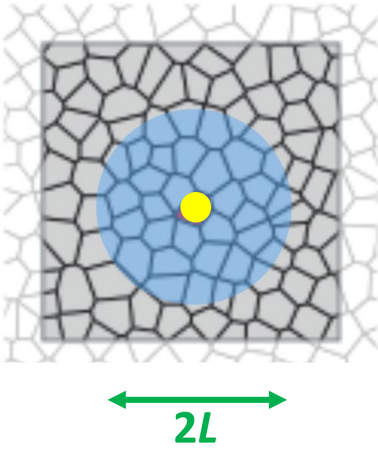






Feedback length scale (L) in the skin is the size of a single cell
= neighbor fate coupling

Feedback length scale can be different across tissues



$L \sim$ single cell level (neighboring feedback)

Signaling through adhesion, Notch-Delta, etc

(ex: skin, intestinal crypt)

$L \sim$ scale of >10 cells

Tissue stretching/compression induced mechanical feedback

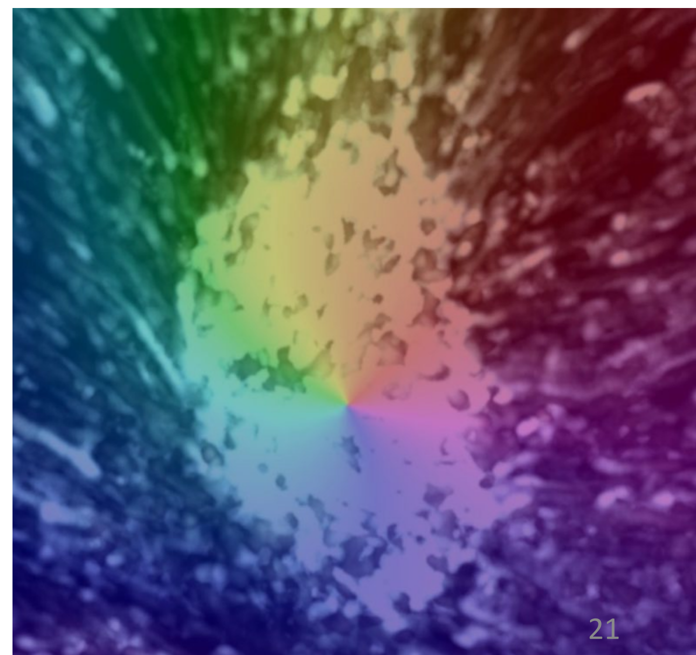
Quorum sensing, growth factor related feedback

(ex: seminiferous tubule 精細管)

2. Topological defects induce cell flow

[With Ryoichiro Kageyama and Masaki Sano, Nature 545 327 (2017)]

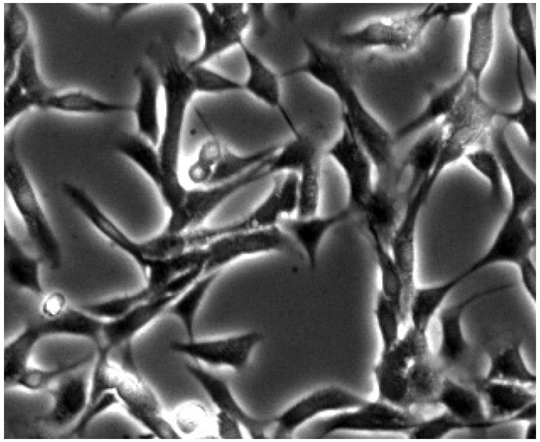
[Ongoing work with Masahito Uwamichi]



Neural stem cells

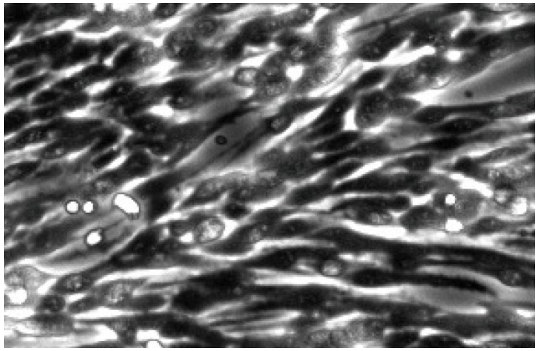
20 um

Phase contrast image



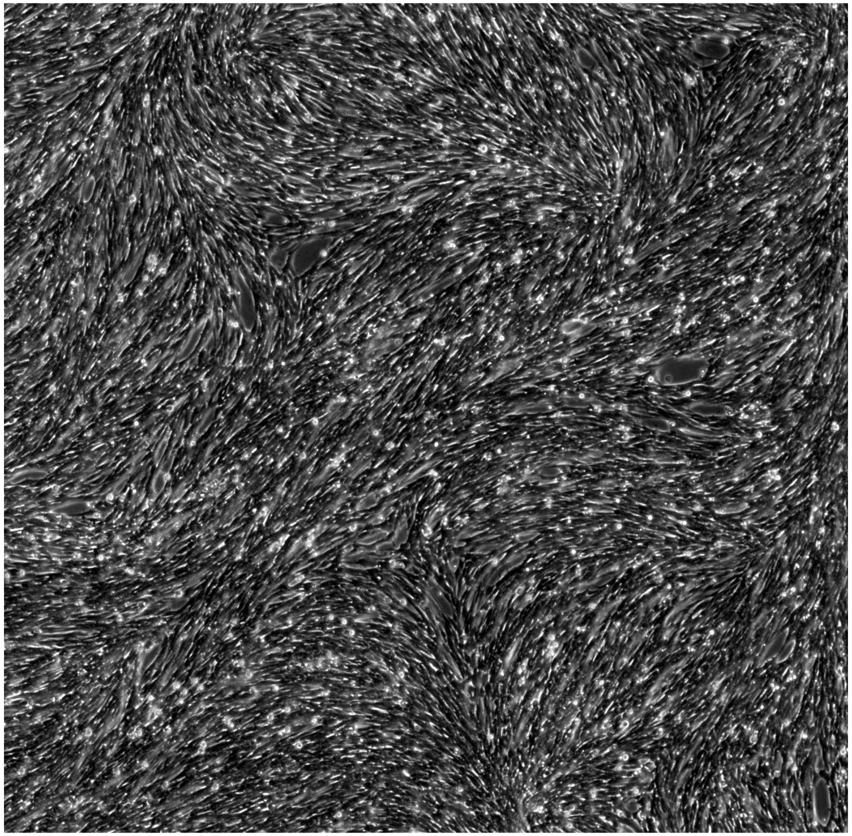
Multipotent and culturable

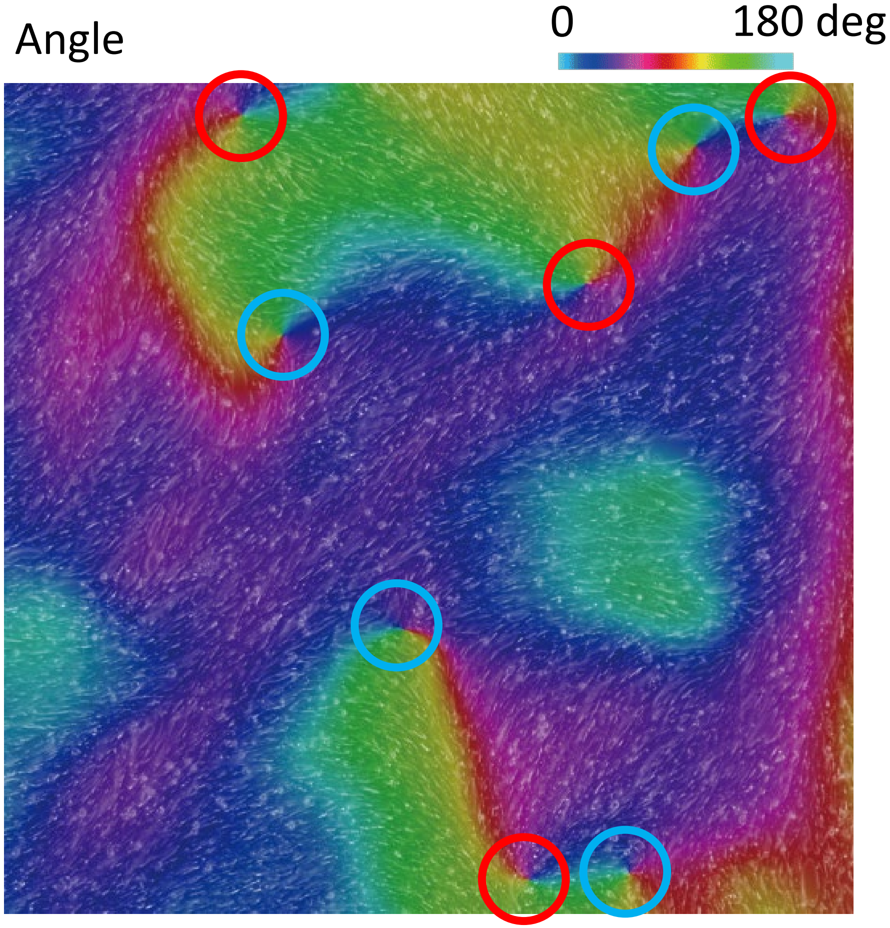
Growth



Local alignment at high density

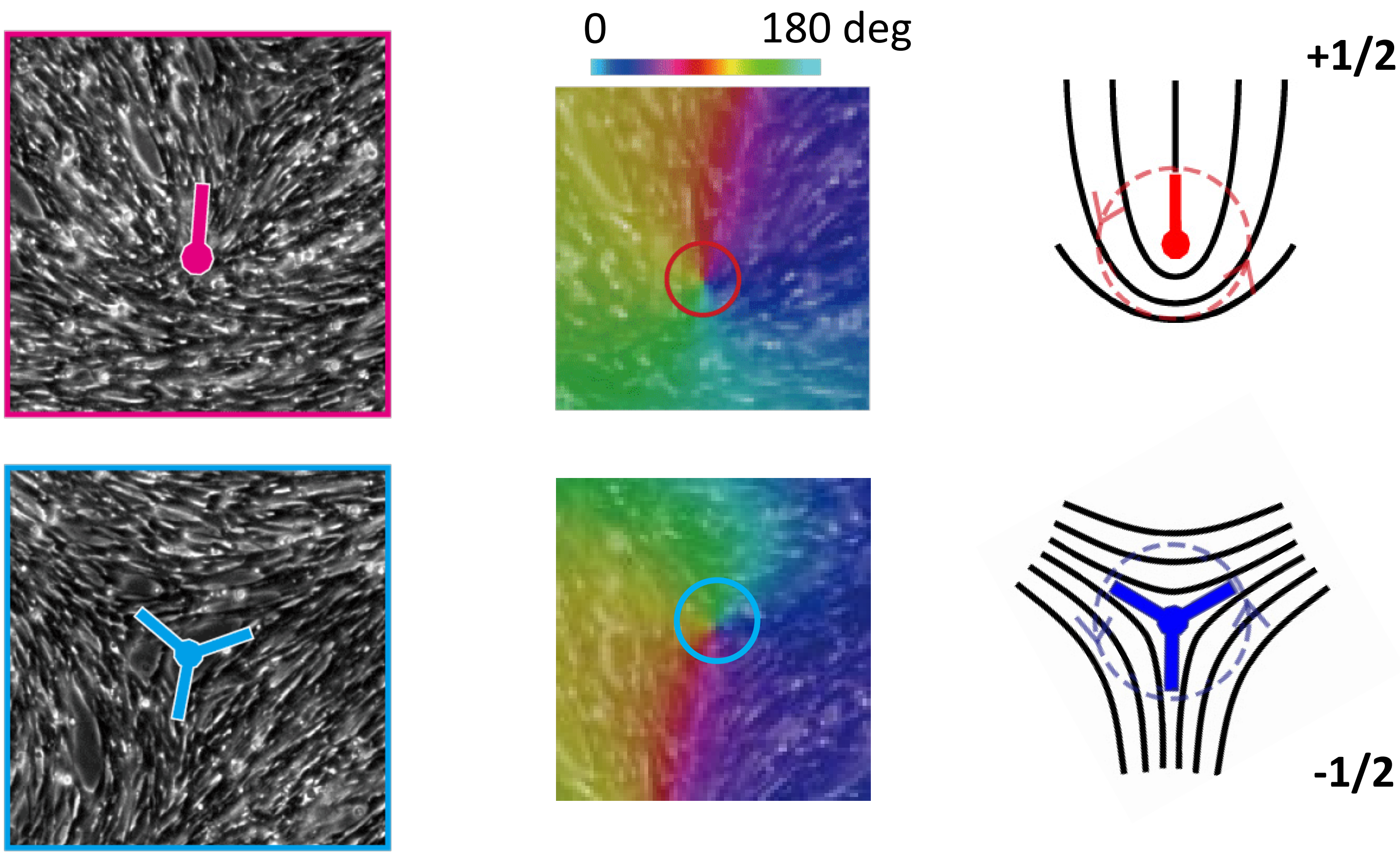
Large scale image





1 mm

Topological defects in cell culture

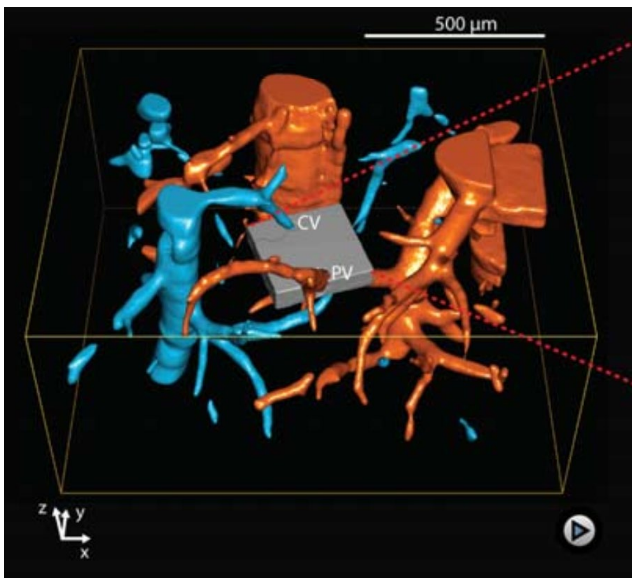


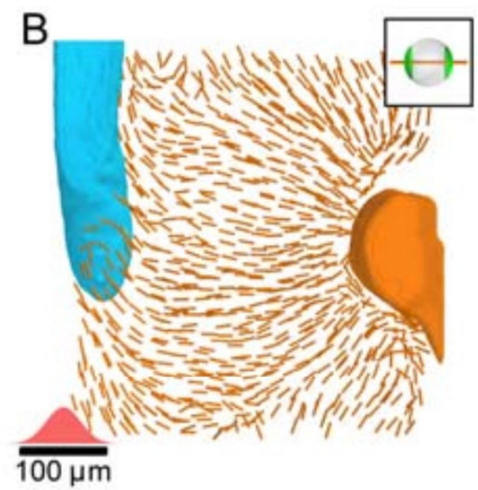
bioRxiv (Dec 13th 2018)

Liquid-crystal organization of liver tissue

Hernan Morales-Navarrete, Hidenori Nonaka, Andre Scholich, Fabian Segovia-Miranda, Walter de Back, Kirstin Meyer, Roman L Bogorad, Victor Koteliansky, Lutz Brusch, Yannis Kalaidzidis, Frank Julicher, Benjamin M. Friedrich, Marino Zerial

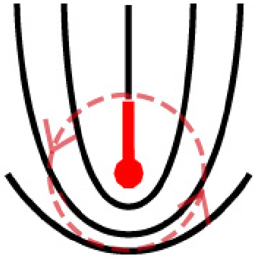
doi: https://doi.org/10.1101/495952

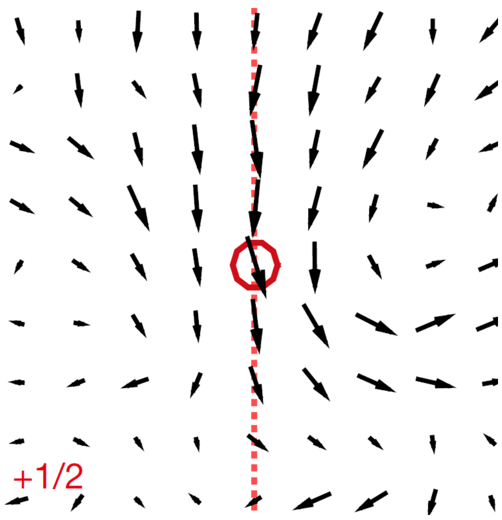


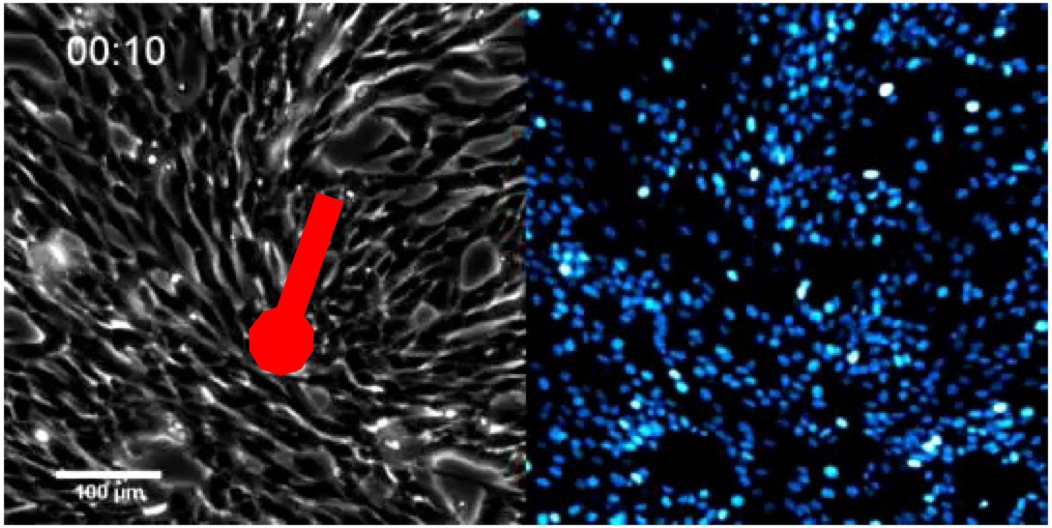


Biopolar cell polarity axis (hepatocytes)

Cell flow was induced by topological defects







+1/2 defect is the “sink”

- 1/2 defect is the “source”

Geometry induced flow in active systems

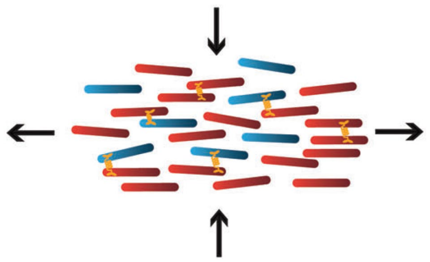
Activity in nematic systems can induce

macroscopic active force = $-\eta \underline{\nabla \cdot Q}$

Spatial inhomogeneity in pattern

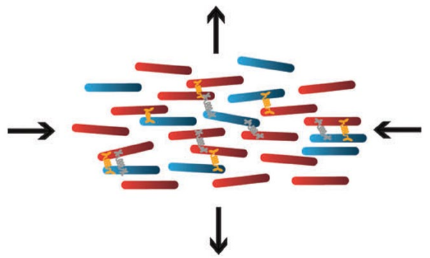
Extensile systems

$\eta > 0$



Contractile systems

$\eta < 0$



Q-tensor
(measures the direction
and extent of ordering)

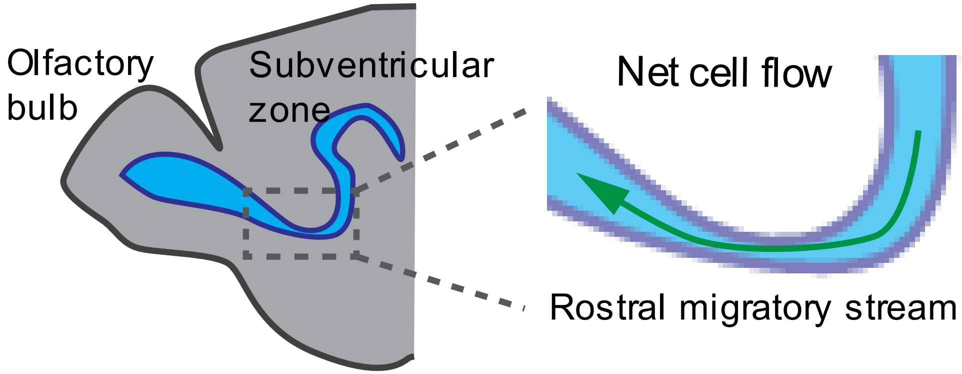
$$Q_{ij} = S(n_i n_j - \delta_{ij}/2)$$

$\eta = 0$ in passive systems

Blackwell et al., Soft Matter (2016)

Geometry driven active transport

Mouse/rat brain:



Summary

- Some concepts in nonequilibrium physics are useful
  in understanding multicellular phenomena

- Cell fate dynamics of skin stem cells
  seem to follow the 2D voter model

- Geometry induced flow in active systems
  as a mechanism of cell flow control

Tissue homeostasis

Experiments:

Kailin Mesa

Katherine Cockburn

David Gonzalez

Valentina Greco

(Yale School of Medicine)

Theory:

Allon M. Klein

Harvard Medical School

Hiroki Yamaguchi

Takahiro Sagawa

Univ. Tokyo

Active neural stem cells

Masaki Sano
Univ. Tokyo

Ryoichiro Kageyama
Kyoto Univ.

Masahito Uwamichi
Univ. Tokyo

Started lab in Kobe

Technical Staffs
Yuko Sakaide
Lisa Yamauchi

From FY 2019
Kyosuke Adachi
Yosuke Fukai
Daiki Nishiguchi

Visiting student
Uwamichi Masahito (U Tokyo) →

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Thank you!