A population dynamics model of cell-cell adhesion and its applications

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joint work with
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KARLSTAD APPLIED ANALYSIS SEMINAR (KAAS)
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Cell adhesion

is the binding of a cell to a surface, such as an extracellular matrix or another cell.

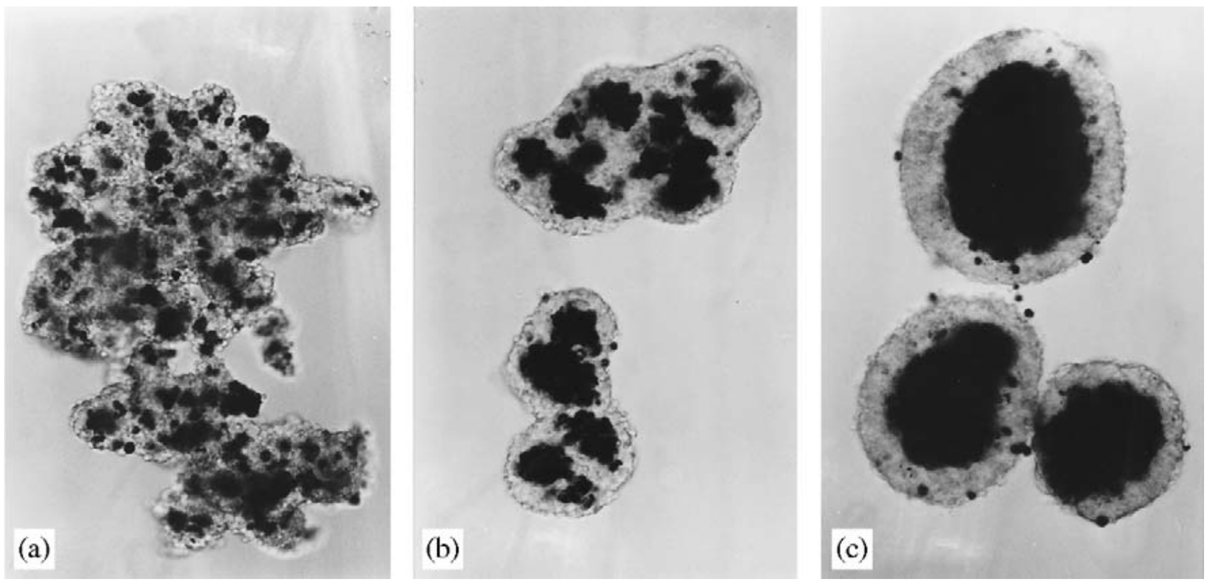
Cell sorting

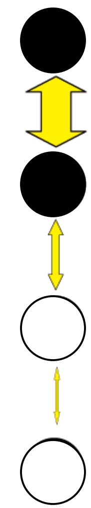
is the ability to separate cells according to their properties.

These processes are essential in organ formation during embryonic development and in maintaining multicellular structure.

cell-cell adhesion & cell sorting

Randomly intermixed two types of cells were cultured.
(a) two types of cell are randomly mixed in the aggregate,
(b) multiple internal black cell clusters embedded in colorless tissue,
(c) the black cells form single central masses completely surrounded by the colorless tissue.





5-hour 19-hour 2-day

Living aggregates of 7-day chick embryo neural retinal and pigmented retinal epithelial cells produced by reaggregation of cells from stirred cell suspensions. Neural retinal cells are colorless, pigmented retinal cells are black.

From Armstrong ('71)

Differential adhesion hypothesis

Steinberg ('63)

A mixture of two cell types may evolve to one of four configurations depending on the relative strengths.

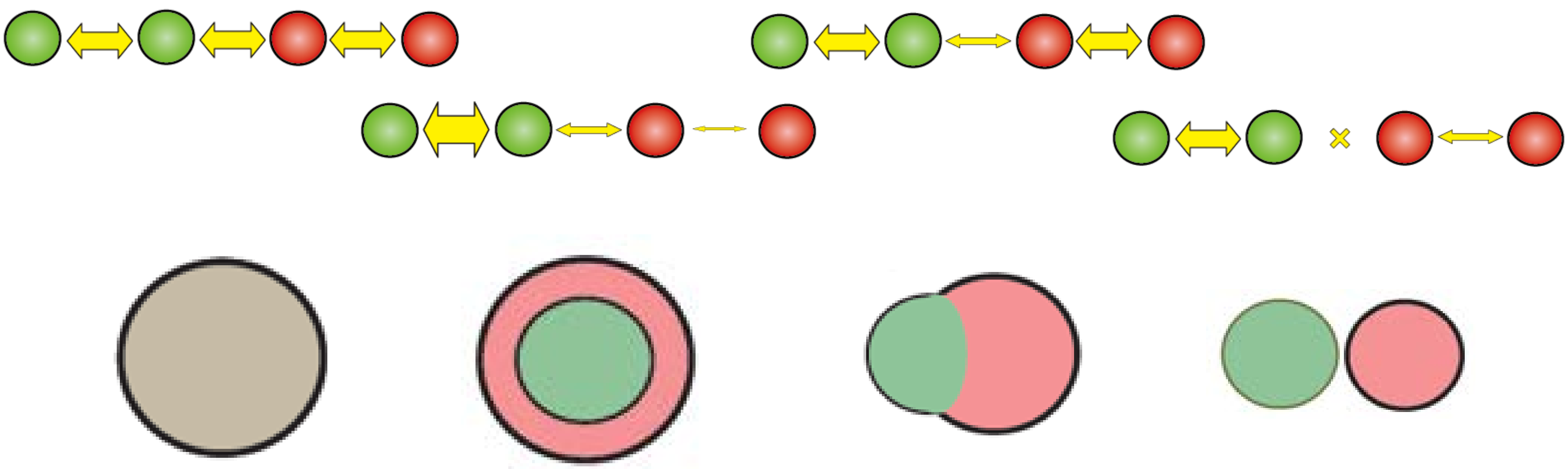
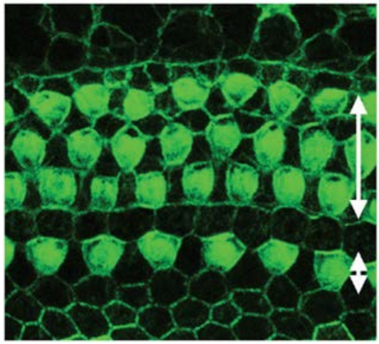


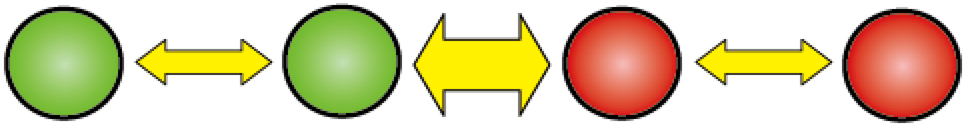
Illustration of how the reversible works of cohesion and adhesion determine the most stable configuration of a liquid system.

From Foty & Steinberg ('04)

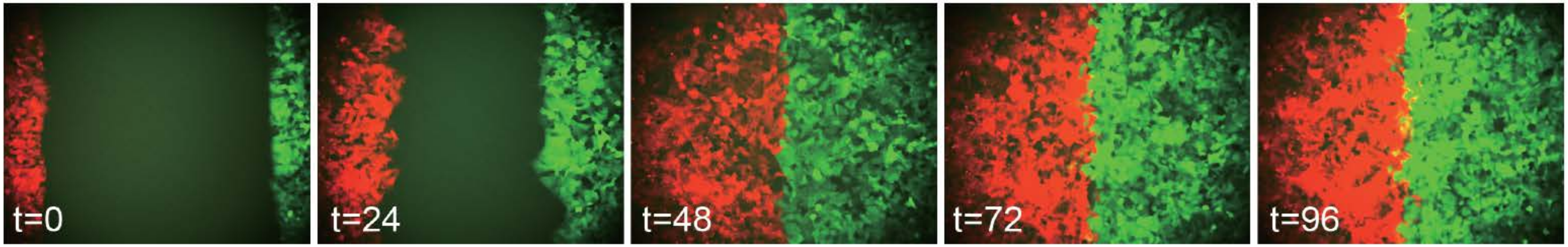
cell-cell adhesion



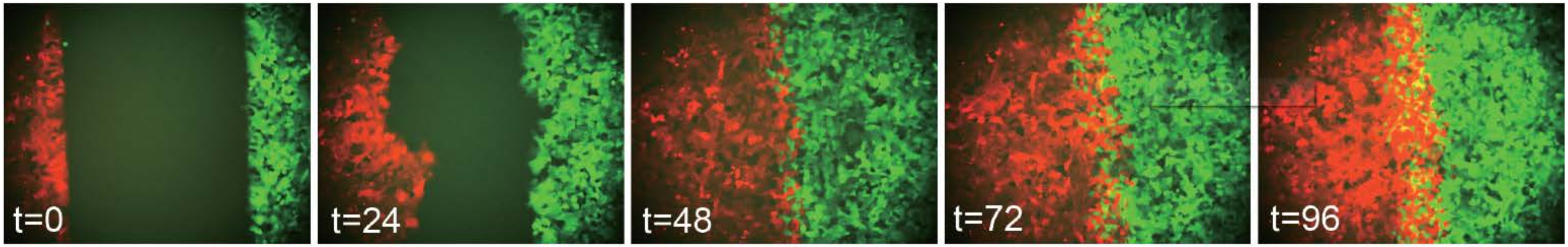
Nectin-1 Nectin-3



Nectin-1 expressing cells Nectin-1 expressing cells



Nectin-1 expressing cells Nectin-3 expressing cells

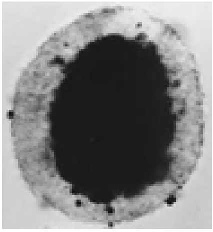


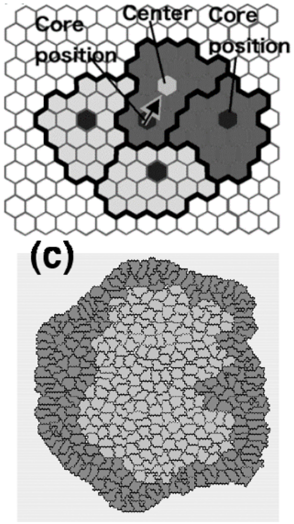
By Hideru Togashi

Computational models

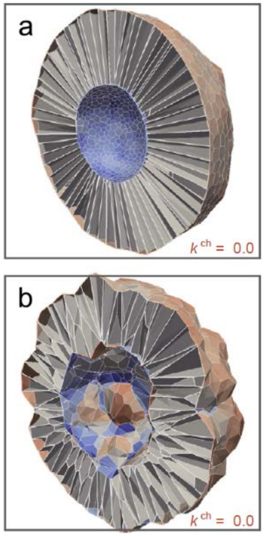
Single-cell-based models

- Cellular Potts models (lattice-based)
  e.g. Graner, Glazier (1992), Chen, Glazier, Izaguirre, Alber (2007), Maeda, Ajioka, Nakajima (2007), Krieg et al. (2008).
- Vertex models (lattice-free)
  e.g. Odell, Oster, Alberch, Burnside (1981), Honda, Yamanaka (1984), Hashimoto, Nagao, Okuda (2018).
- Other lattice-free models
  e.g. Sulsky, Childress, Percus (1984), Palsson, Othmer (2000).





Maeda et al. ('07)

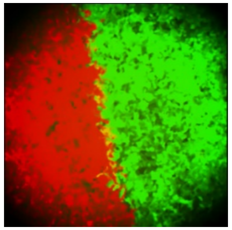


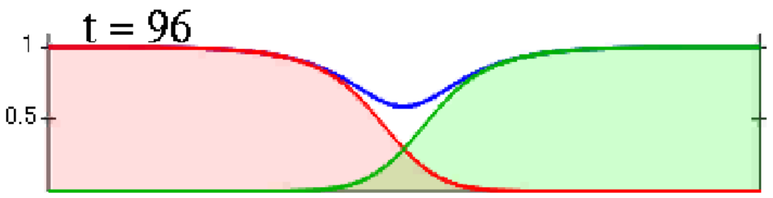
Okuda et al. ('13)

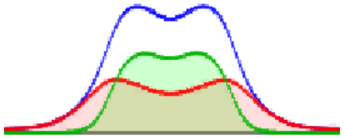
A model for population densities

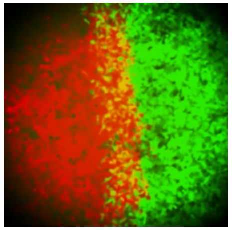
- Armstrong, Painter, Sherratt (2006)

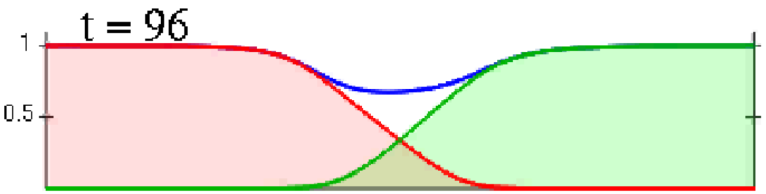
$$
\begin{cases}
\dfrac{\partial u}{\partial t} = \Delta u - \nabla \cdot (u K_1(u,v)), \\
\dfrac{\partial v}{\partial t} = \Delta v - \nabla \cdot (v K_2(u,v)).
\end{cases}
$$









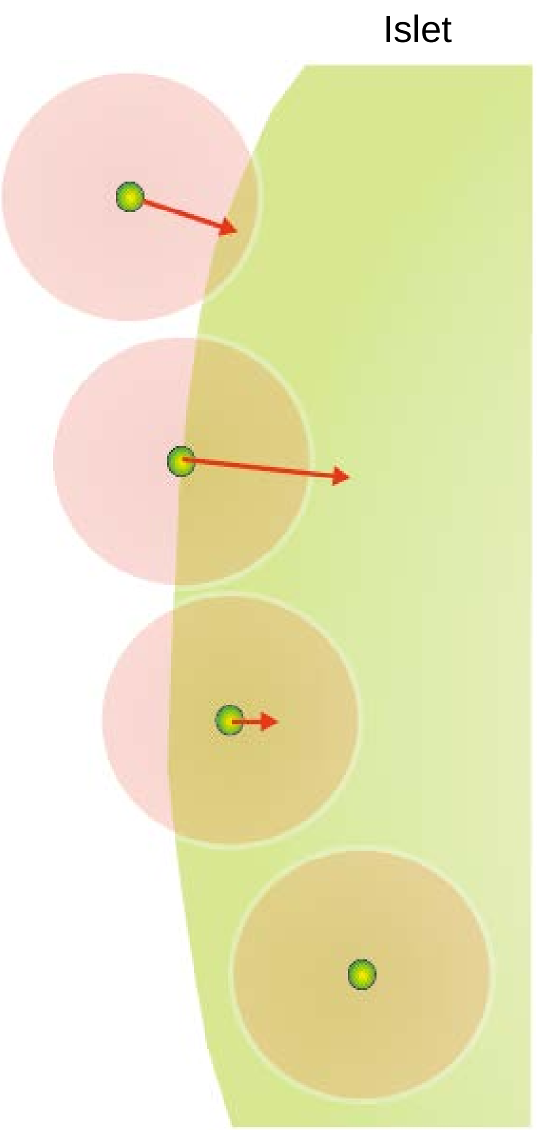


Armstrong-Painter-Sherratt model (1c)

$$\frac{\partial u}{\partial t} = \Delta u - \nabla \cdot (u \boldsymbol{K}_g(u)) .$$

$$\boldsymbol{K}_g(u)(\boldsymbol{x}) = \int_0^R \int_{S^{d-1}} a\, g(u(\boldsymbol{x} + r\boldsymbol{\eta}))\, \omega(r) r^{d-1} \boldsymbol{\eta}\, d\boldsymbol{\eta} dr.$$

$$g(u) = \begin{cases} u(1 - u/m) & \text{if} \quad u < m, \\ 0 & \text{otherwise.} \end{cases}$$



- R : sensing radius,
- a : adhesive strength parameter,
- g : force magnitude on the adhesivity,
- m : crowding capacity,
- ω : force magnitude on the distance from x,
- η : direction of the force; outer unit normal to the circle.

Armstrong-Painter-Sherratt model (2c)

$$\begin{cases} \dfrac{\partial u}{\partial t} = \Delta u - \nabla \cdot (u \boldsymbol{K}_{g1}(u,v)) \\ \dfrac{\partial v}{\partial t} = \Delta v - \nabla \cdot (v \boldsymbol{K}_{g2}(u,v)) \end{cases}$$

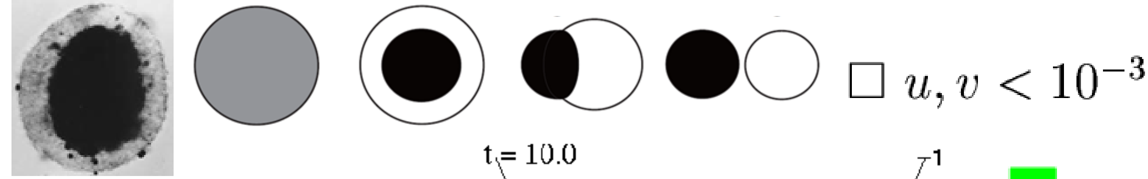
$$\boldsymbol{K}_{g1}(u,v)(\boldsymbol{x}) = \int_0^1 \int_{S^{d-1}} \Big[a_{11} g_{11}(u(\boldsymbol{x}+r\boldsymbol{\eta}), v(\boldsymbol{x}+r\boldsymbol{\eta})) + a_{12} g_{12}(u(\boldsymbol{x}+r\boldsymbol{\eta}), v(\boldsymbol{x}+r\boldsymbol{\eta})) \Big] \omega(r) r^{d-1} \boldsymbol{\eta}\, d\boldsymbol{\eta} dr,$$

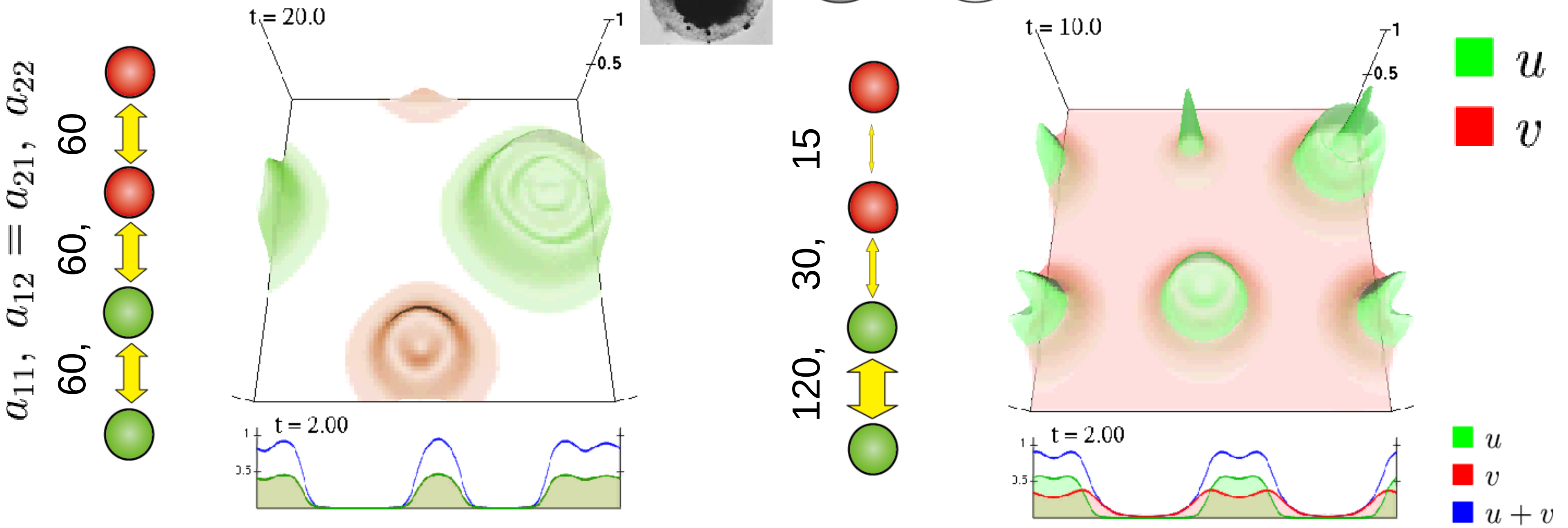
$$\boldsymbol{K}_{g2}(u,v)(\boldsymbol{x}) = \int_0^1 \int_{S^{d-1}} \Big[a_{21} g_{21}(u(\boldsymbol{x}+r\boldsymbol{\eta}), v(\boldsymbol{x}+r\boldsymbol{\eta})) + a_{22} g_{22}(u(\boldsymbol{x}+r\boldsymbol{\eta}), v(\boldsymbol{x}+r\boldsymbol{\eta})) \Big] \omega(r) r^{d-1} \boldsymbol{\eta}\, d\boldsymbol{\eta} dr.$$

$$g_{11}(u,v) = g_{21}(u,v) = \begin{cases} u(1-u-v) & \text{if } \; u+v<1, \\ 0 & \text{otherwise.} \end{cases}$$

$$g_{22}(u,v) = g_{12}(u,v) = \begin{cases} v(1-u-v) & \text{if } \; u+v<1, \\ 0 & \text{otherwise.} \end{cases}$$

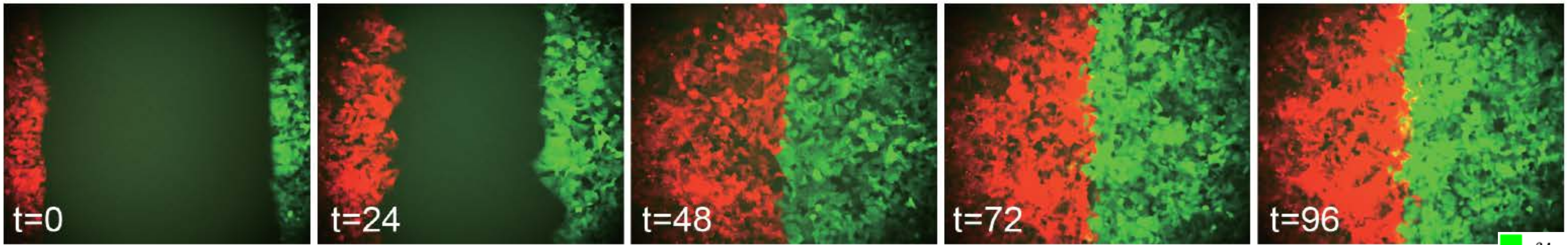
Numerical simulations





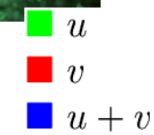
Steinberg noted that
properties of sorting-out cell systems are similar to those of two-phase systems of mutually immiscible liquids such as oil and water.

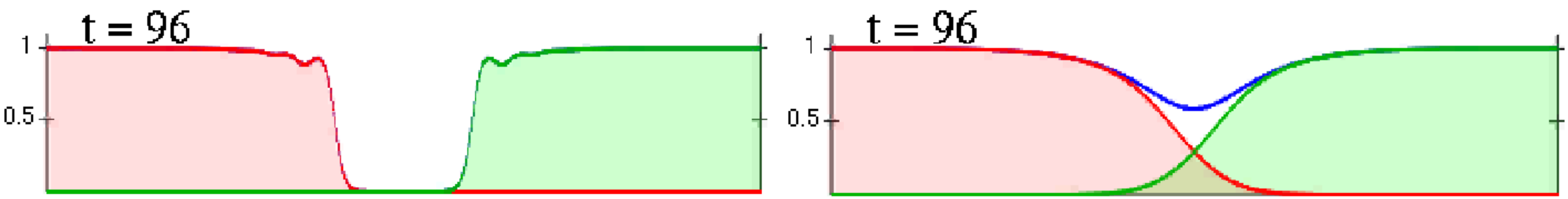
Numerical simulations (+growth term)

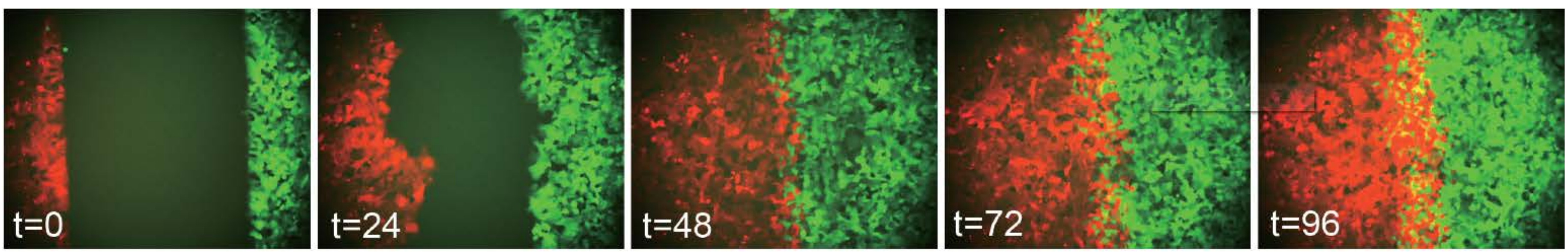


30, 30, 30

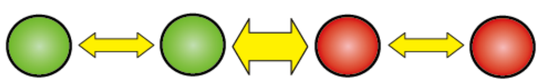
Large diff. coef.

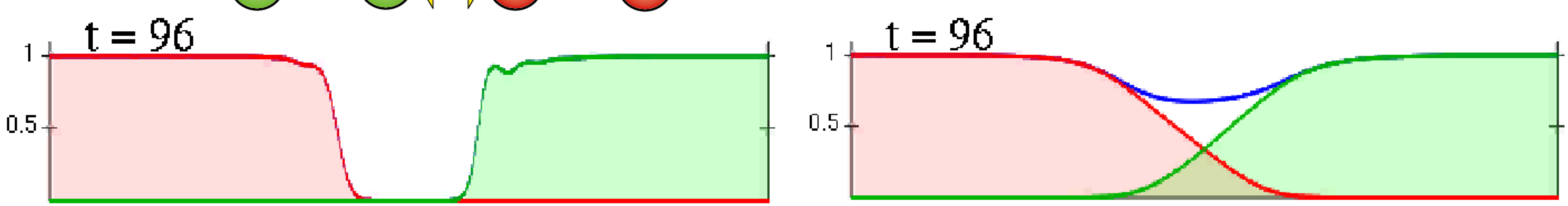




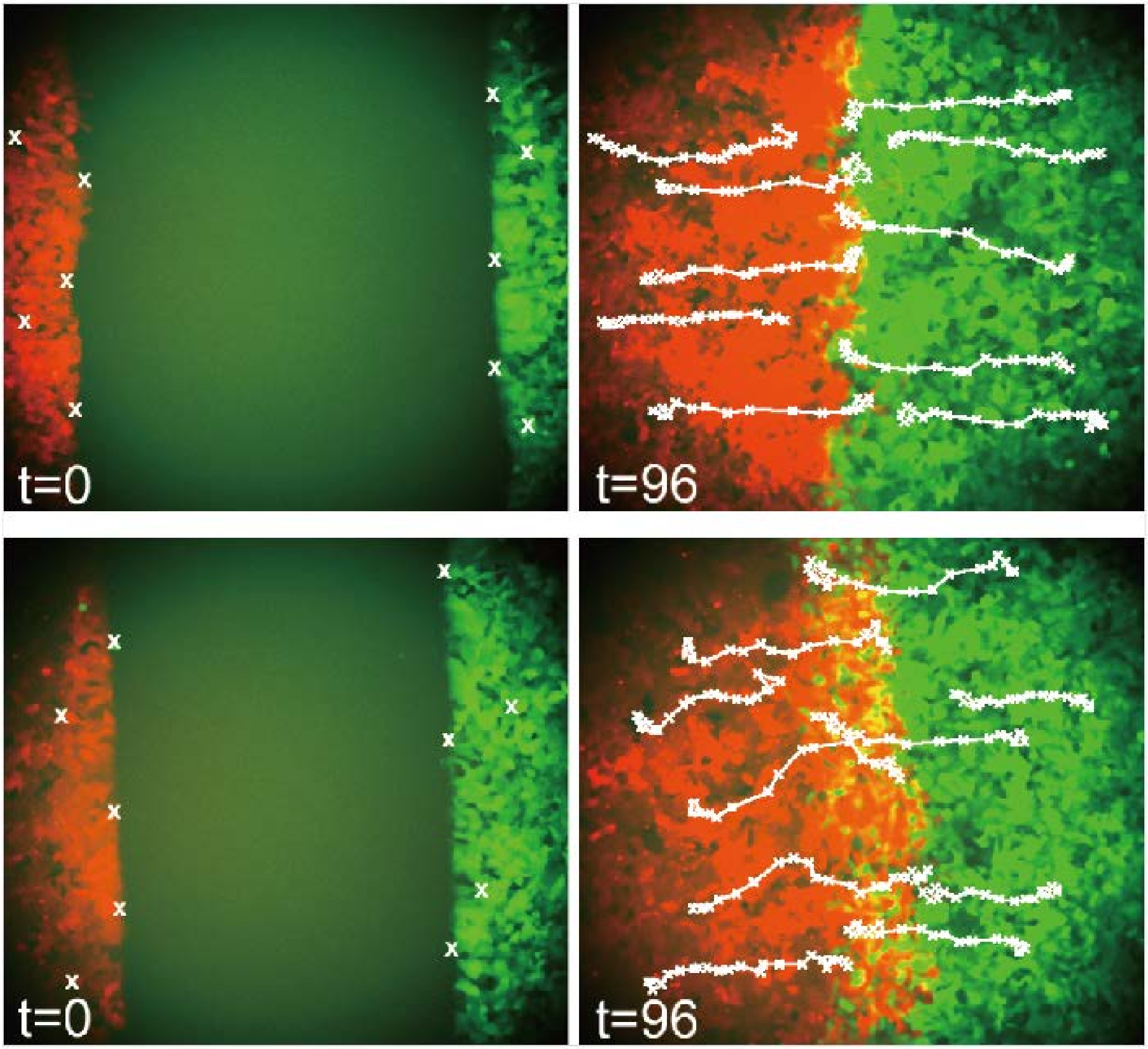


30, 230, 8





cell-cell adhesion



A model of cell-cell adhesion (1c)

$$\frac{\partial u}{\partial t} = -\nabla \cdot (u\boldsymbol{V}),$$

$$\boldsymbol{V} = \boldsymbol{V}_p + \boldsymbol{V}_a.$$

u : population density

$\boldsymbol{V}_p$: velocity due to pressure

$$\boldsymbol{V}_p = -\nabla p = -c_p \nabla u.$$

c_p : dispersivity,

$\boldsymbol{V}_a$: velocity due to adhesion

Velocity due to adhesion

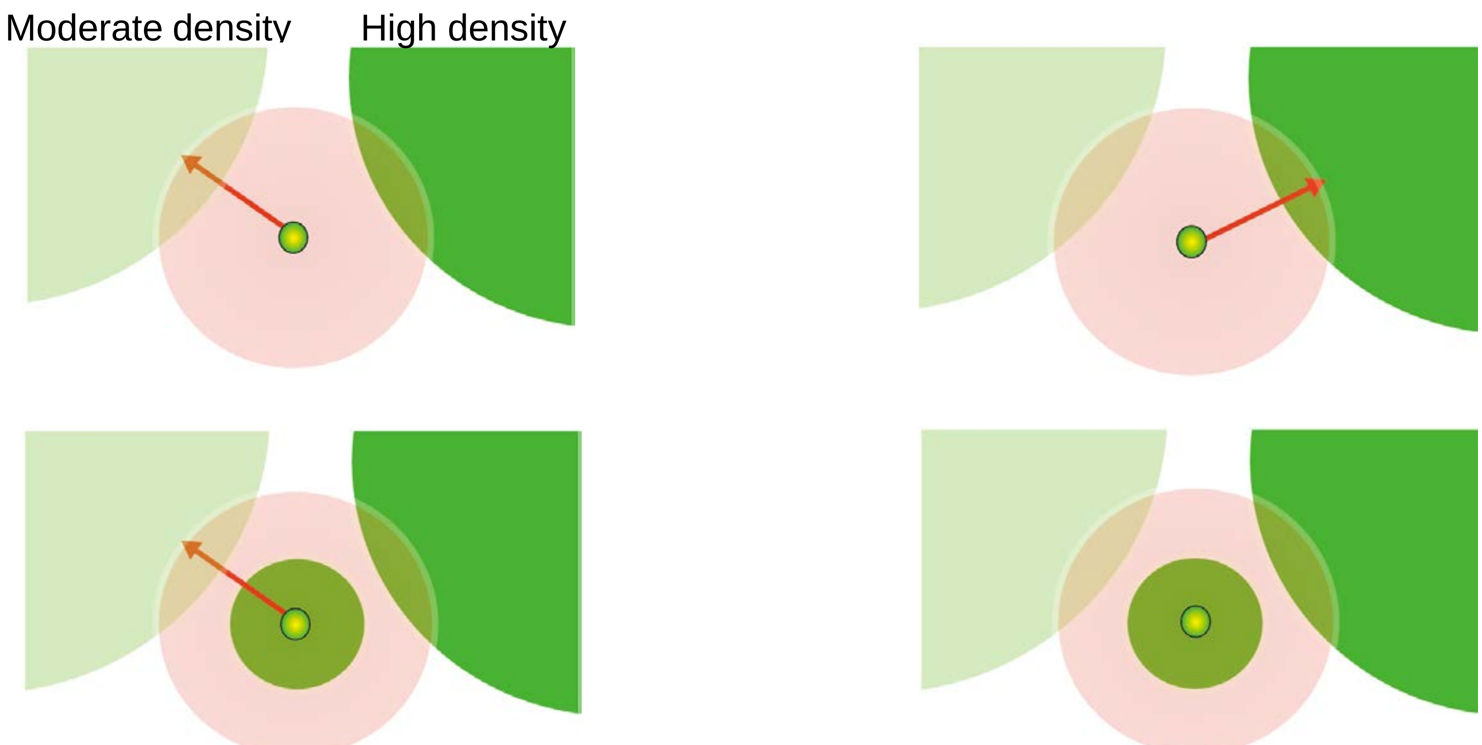
Armstrong-Painter-Sherratt ('06)

$$\boldsymbol{K}_g(u)(\boldsymbol{x}) = \int_0^1 \int_{S^{d-1}} a g(u(\boldsymbol{x} + r\boldsymbol{\eta}))\, \omega(r) r^{d-1} \boldsymbol{\eta}\, d\boldsymbol{\eta} dr.$$

$$\boldsymbol{V}_a = (1 - u/m)\boldsymbol{K}(u)(\boldsymbol{x})$$

$$g(u) = \begin{cases} u(1 - u/m) & \text{if } \quad u < m, \\ 0 & \text{otherwise.} \end{cases}$$

$$\boldsymbol{K}(u)(\boldsymbol{x}) = \int_0^1 \int_{S^{d-1}} a u(\boldsymbol{x} + r\boldsymbol{\eta})\, \omega(r) r^{d-1} \boldsymbol{\eta}\, d\boldsymbol{\eta} dr.$$



A model of cell-cell adhesion (1c)

Rescaling suitably, we obtain

$$\frac{\partial u}{\partial t} = \nabla \cdot (u \nabla u) - \nabla \cdot (u(1-u)\boldsymbol{K}(u)).$$

$$\boldsymbol{K}(u)(\boldsymbol{x}) = \int_0^1 \int_{S^{d-1}} a\, u(\boldsymbol{x} + r\boldsymbol{\eta})\, \omega(r) r^{d-1} \boldsymbol{\eta}\, d\boldsymbol{\eta} dr.$$

Armstrong-Painter-Sherratt model

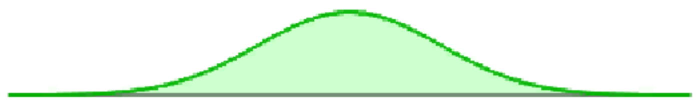
$$\frac{\partial u}{\partial t} = \Delta u - \nabla \cdot (u \boldsymbol{K}_g(u)) \,. \qquad g(u) = \begin{cases} u(1-u/m) & \text{if } \; u < m, \\ 0 & \text{otherwise.} \end{cases}$$

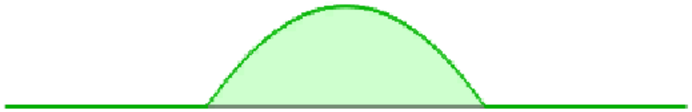
$$\boldsymbol{K}_g(u)(\boldsymbol{x}) = \int_0^1 \int_{S^{d-1}} a\, g(u(\boldsymbol{x} + r\boldsymbol{\eta}))\, \omega(r) r^{d-1} \boldsymbol{\eta}\, d\boldsymbol{\eta} dr$$

Numerical simulations

$$\frac{\partial u}{\partial t} = \Delta u.$$

$$\frac{\partial u}{\partial t} = \nabla \cdot (u \nabla u)\,.$$

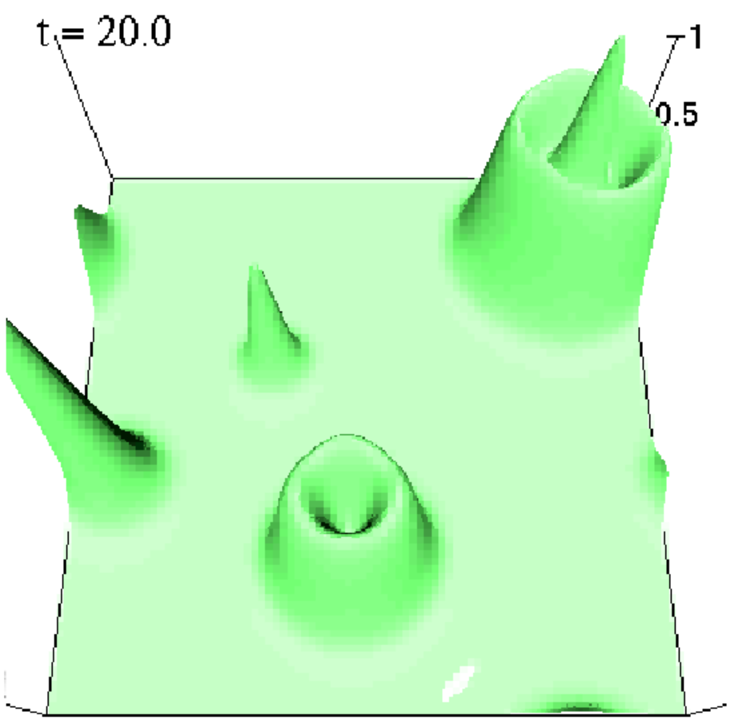


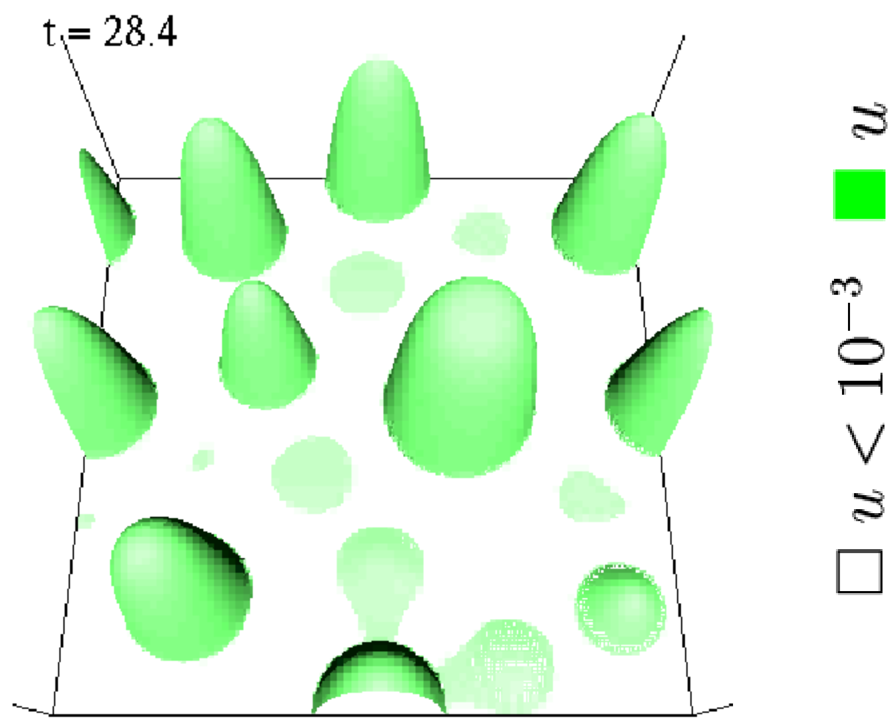


Finite speed of propagation

$$\frac{\partial u}{\partial t} = \Delta u - \nabla \cdot (u K(u))\,.$$

$$\frac{\partial u}{\partial t} = \nabla \cdot (u \nabla u) - \nabla \cdot (u(1-u)\boldsymbol{K}(u)).$$



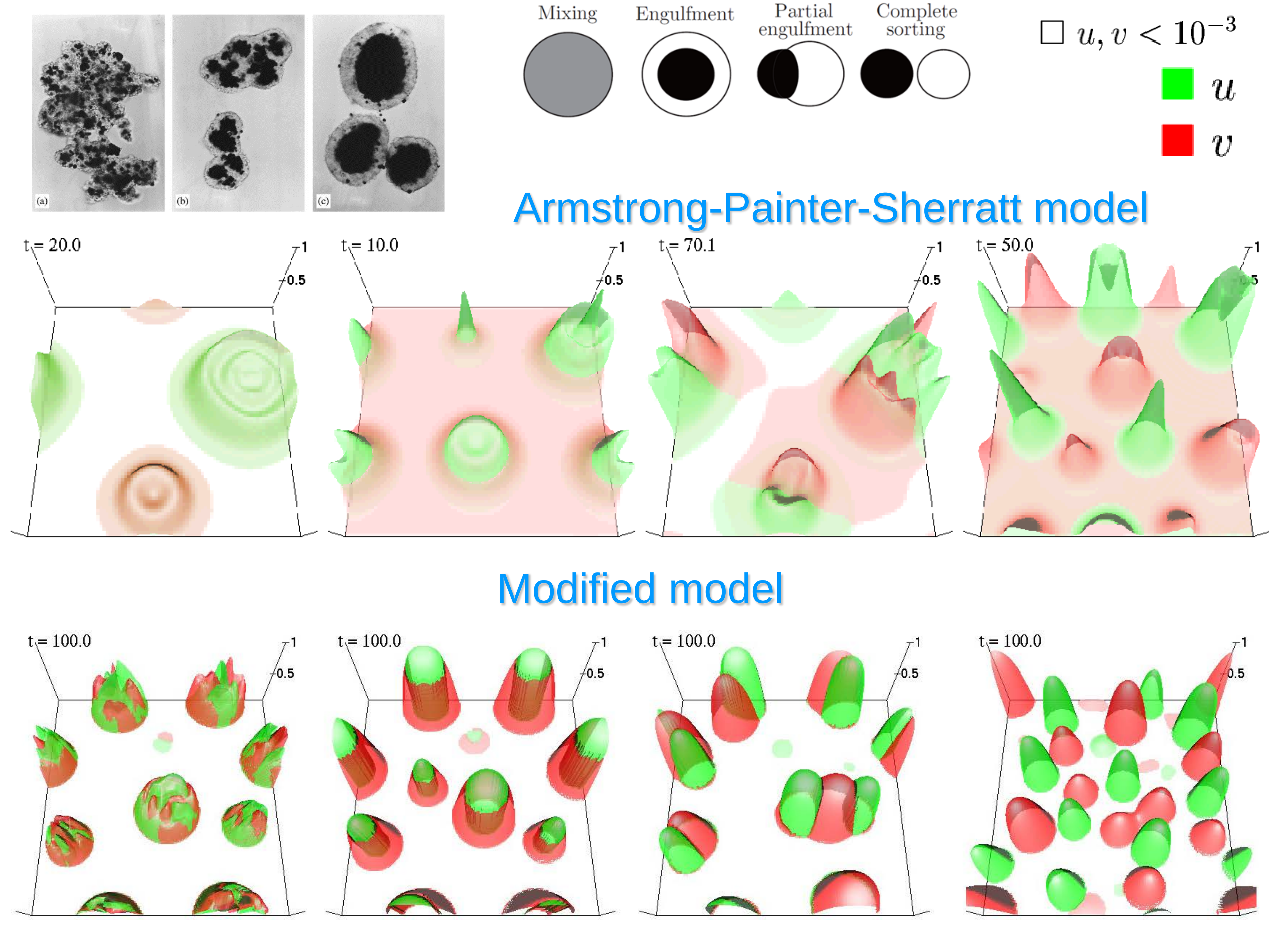


A model of cell-cell adhesion (2c)

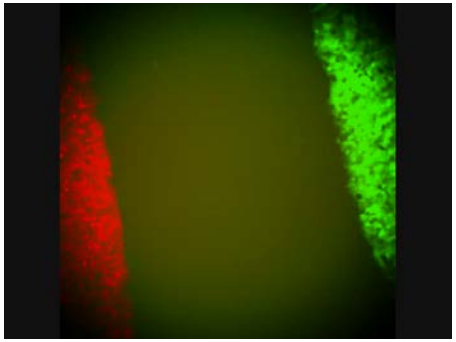
$$\begin{cases} \dfrac{\partial u}{\partial t} = \nabla \cdot (u \nabla (u+v)) - \nabla \cdot (u(1-u-v)\boldsymbol{K}_1(u,v)) \\ \dfrac{\partial v}{\partial t} = \nabla \cdot (v \nabla (u+v)) - \nabla \cdot (v(1-u-v)\boldsymbol{K}_2(u,v)) \end{cases}$$

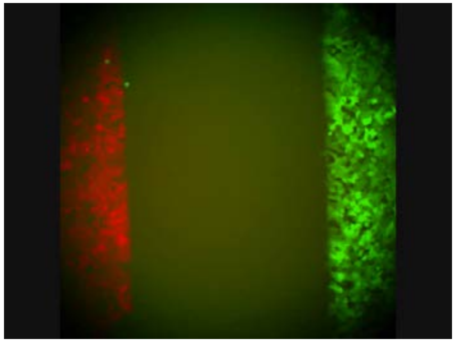
$$\boldsymbol{K}_1(u,v)(\boldsymbol{x}) = \int_0^1 \int_{S^{d-1}} \Big[a_{11} u(\boldsymbol{x} + r\boldsymbol{\eta}) + a_{12} v(\boldsymbol{x} + r\boldsymbol{\eta}) \Big] \omega(r) r^{d-1} \boldsymbol{\eta} \, d\boldsymbol{\eta} dr,$$

$$\boldsymbol{K}_2(u,v)(\boldsymbol{x}) = \int_0^1 \int_{S^{d-1}} \Big[a_{21} u(\boldsymbol{x} + r\boldsymbol{\eta}) + a_{22} v(\boldsymbol{x} + r\boldsymbol{\eta}) \Big] \omega(r) r^{d-1} \boldsymbol{\eta} \, d\boldsymbol{\eta} dr.$$

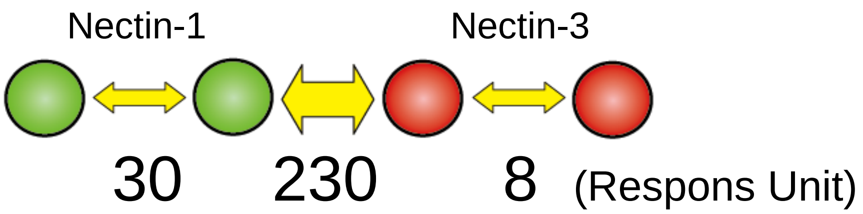

(a)
(b)
(c)
Mixing
Engulfment
Partial engulfment
Complete sorting
$u, v < 10^{-3}$
u
v
Armstrong-Painter-Sherratt model
t = 20.0
1
0.5
t = 10.0
1
0.5
t = 70.1
1
0.5
t = 50.0
1
Modified model
t = 100.0
1
0.5
t = 100.0
1
0.5
t = 100.0
1
0.5
t = 100.0
1
0.5

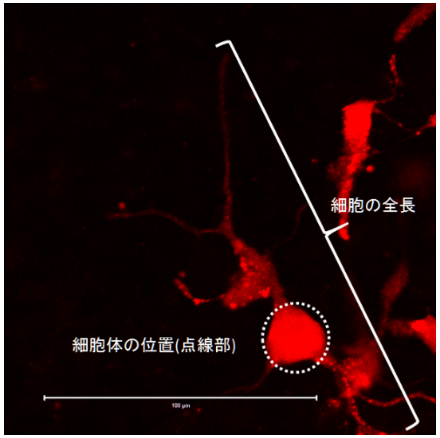
NS for Togashi et al. experiments





Dispersivity: c_p = 100 μm^3/h
Sensing rad.: R = 100 μm
Carrying caps.: $k_1=k_2$ = 0.0748 cells/μm
Birth rates: $b_1=b_2$ = 2/24 times/h
Distance of the initial well: 500 μm
Adhesive strength params.:

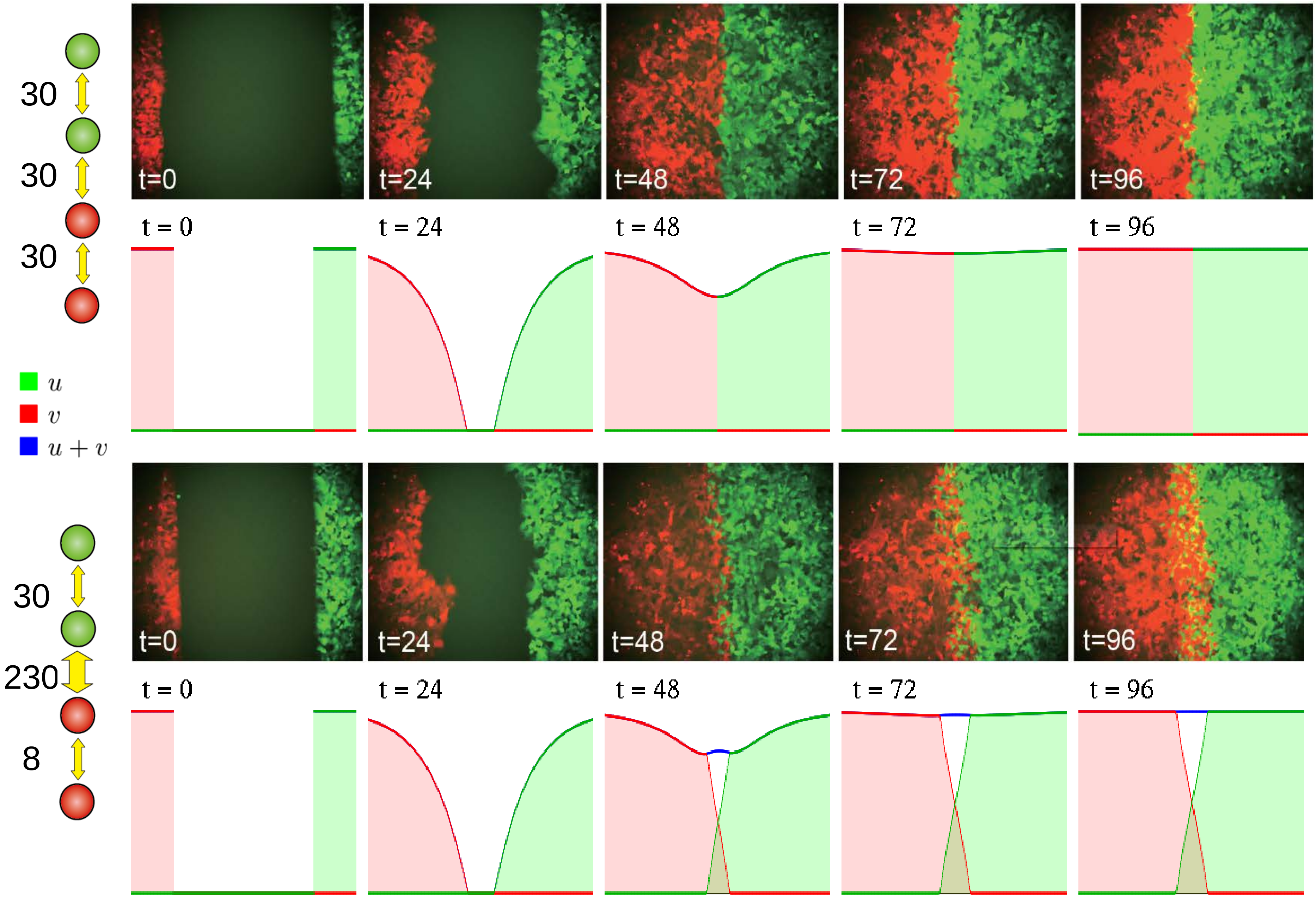




Length of the comp. domain: 2400 μm
Dirichret B.C.

Const. related to viscosity:φ=0.2
Crowding caps.: $m_1=m_2 := k_1=k_2$

Numerical simulations



Application 1

Role of Reelin during Layer Formation in the Cerebral Neocortex

joint work with

Y. Matsunaga*, M. Noda*, K. Hayashi*,
A. Nagasaka**, S. Inoue*, T. Miyata**,
T. Miura***, K. Kubo*, K. Nakajima*

* Keio Univ. (Med.)
** Nagoya Univ. (Med.)
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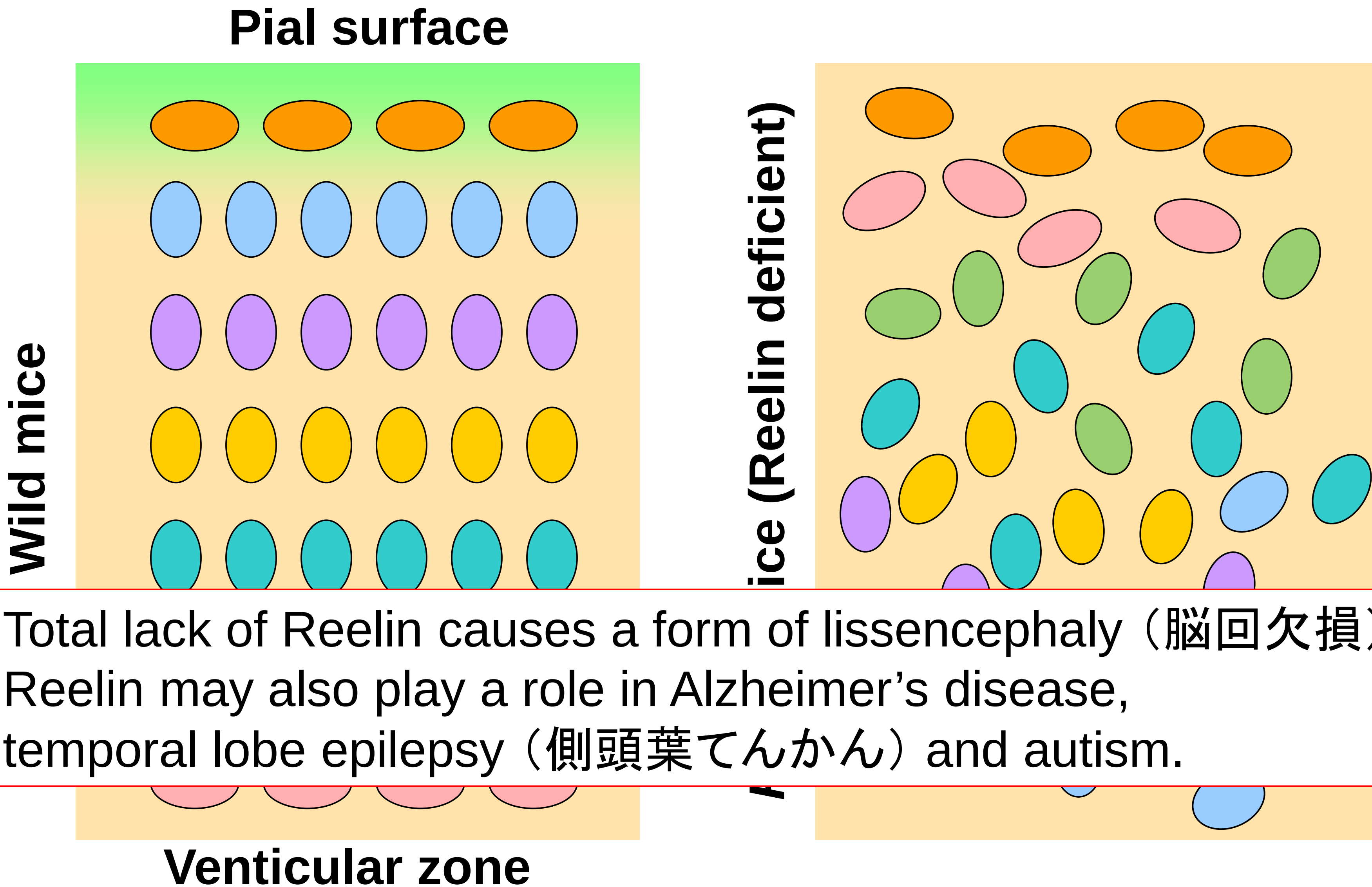
PNAS('17)

Reelin is an essential glycoprotein for the establishment of a highly organized 6-layered structure of neurons of the mammalian neocortex.



Total lack of Reelin causes a form of lissencephaly（脳回欠損）.
Reelin may also play a role in Alzheimer’s disease,
temporal lobe epilepsy（側頭葉てんかん）and autism.

Role of Reelin?

It has long been thought that Reelin is a stop signal for migrating neocortical neurons because the neurons stop just beneath Reelin-rich regions.

Nakajima's group revealed that ectopic expression of Reelin caused neuronal aggregation. They found that neurons were densely packed in the outermost region of the developing cortex.

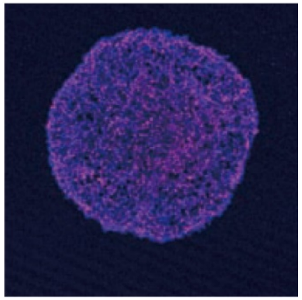
Does Reelin directly promote adhesion among neurons?

Does Reelin directly promote adhesion?

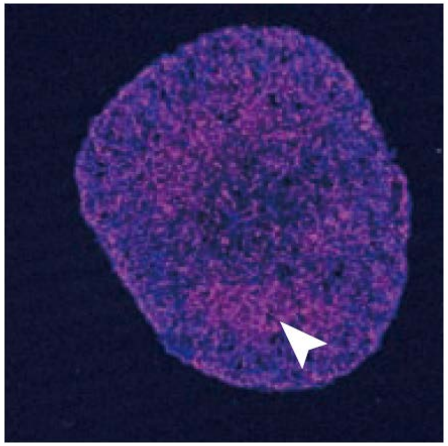
To uncover how Reelin controls the intercellular adhesion among cortical cells, Nakajima’s group performed Reelin stimulation experiments using *in vitro* primary cortical neurons.

Experiments

Mock (Reelin -)

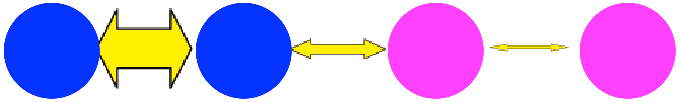


Reelin +

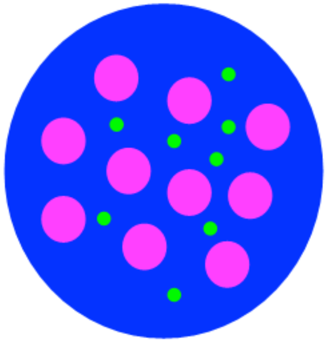


Neurons

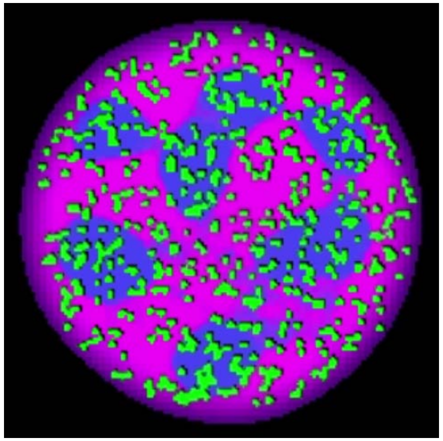
Stem cells



Image



Numerical Exp.



Why?

Model

Stem $$\frac{\partial u}{\partial t} = \underbrace{\nabla\cdot(u\nabla(u+v+w))}_{\text{dispersion}} - \underbrace{\nabla\cdot(u\boldsymbol{K}_1(u,v,w))}_{\text{cell-cell adhesion}} + \underbrace{c_1 u}_{\text{proliferation}} - \underbrace{c_2 u}_{\text{to immature neuron}},$$

Immature neuron $$\frac{\partial v}{\partial t} = \nabla\cdot(v\nabla(u+v+w)) - \nabla\cdot(v\boldsymbol{K}_2(u,v,w)) + \underbrace{c_2 u}_{\text{from RGC}} - \underbrace{c_3 v}_{\text{to mature neuron}},$$

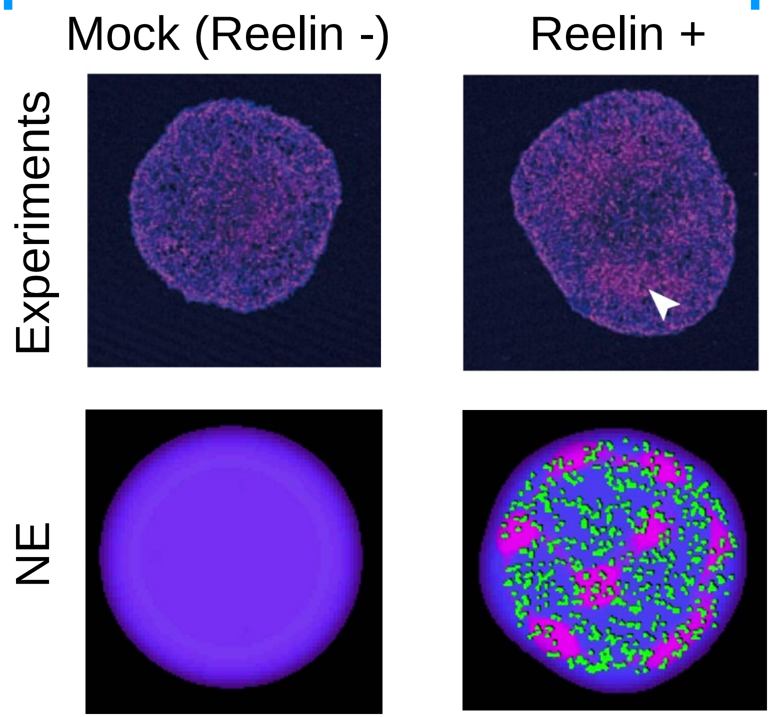
Mature neuron $$\frac{\partial w}{\partial t} = \nabla\cdot(w\nabla(u+v+w)) - \nabla\cdot(w\boldsymbol{K}_3(u,v,w)) + \underbrace{c_3 v}_{\text{from immature neuron}}.$$

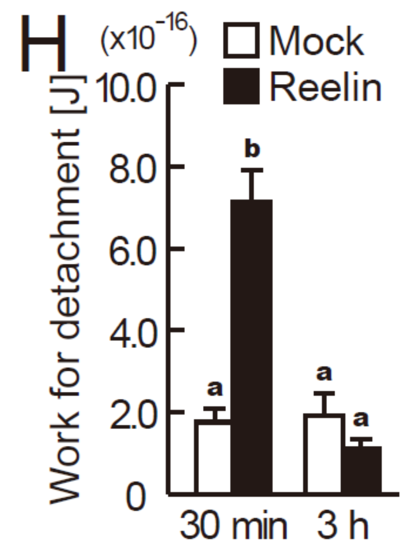
$$\boldsymbol{K}_i(u,v,w)(\boldsymbol{x}) = \frac{1}{R}\int_0^R \int_{S^1}[a_{i1}g_{i1}(u,v,w) + a_{i2}(r)g_{i2}(u,v,w) + a_{i3}g_{i3}(u,v,w)](\boldsymbol{x}+s\boldsymbol{\eta})s\boldsymbol{\eta}\, d\boldsymbol{\eta}\, ds$$

Adhesion strength	u	v	w
u	10	10	8
v	10	10+20r	8
w	8	8	8

Numerical Experiments and Experiments

Adhesion strength	u	v	w
u	10	10	8
v	10	10+20r	8
w	8	8	8





Reelin transiently (and not persistently) promotes N-cadherin-mediated neuronal aggregation.
When N-cadherin and stabilized β-catenin were overexpressed in the migrating neurons, the transfected neurons were abnormally distributed in the superficial region of the neocortex.

Transient but not persistent increase in cell-cell adhesion might be necessary for the highly organized layered structure of neurons in the mammalian neocortex.

Application 2

Role of Differential Adhesion during Columnar Unit Formation in the Drosophila brain

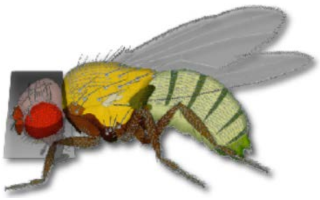
joint work with

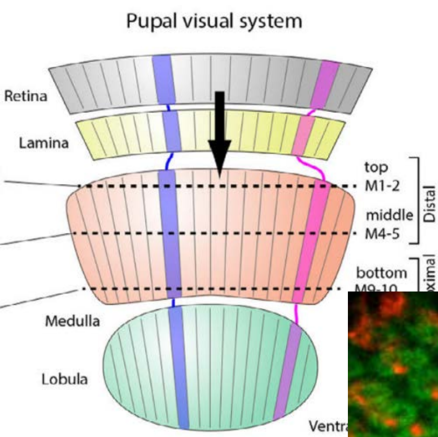
O. Trush[1], C. Liu[1], X. Han[1], Y. Nakai[1], R. Takayama[1], J.A. Carrillo[2], H. Takechi[3], S. Hakeda-Suzuki[3], T. Suzuki[3] and M. Sato[1]

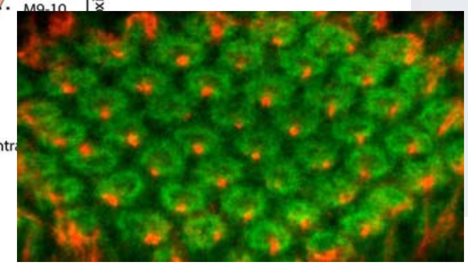
[1]Kanazawa Univ. (Med.)
[2]Imperial College London (Math.),
[3]Tokyo Inst. Tech. (Life Sci.)

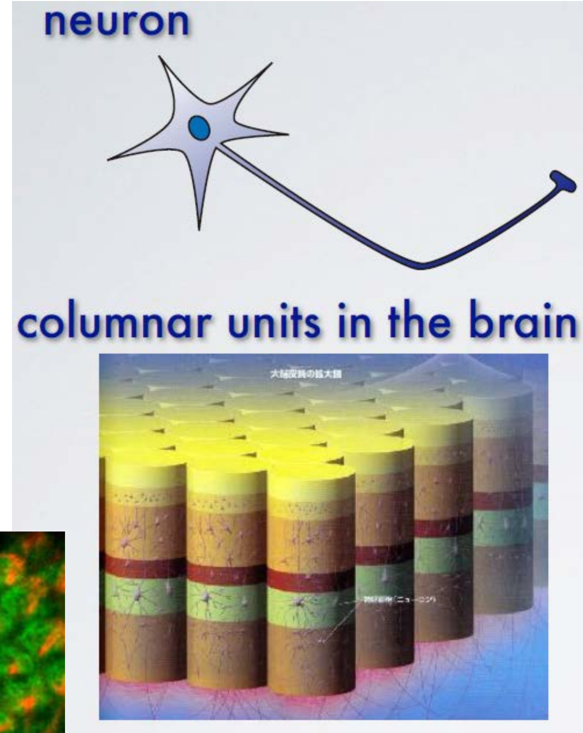
Submitted

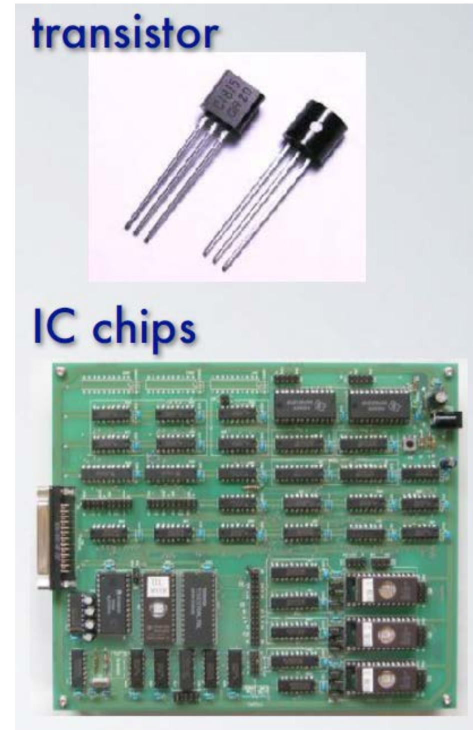
Columnar Structure in the Drosophila brain









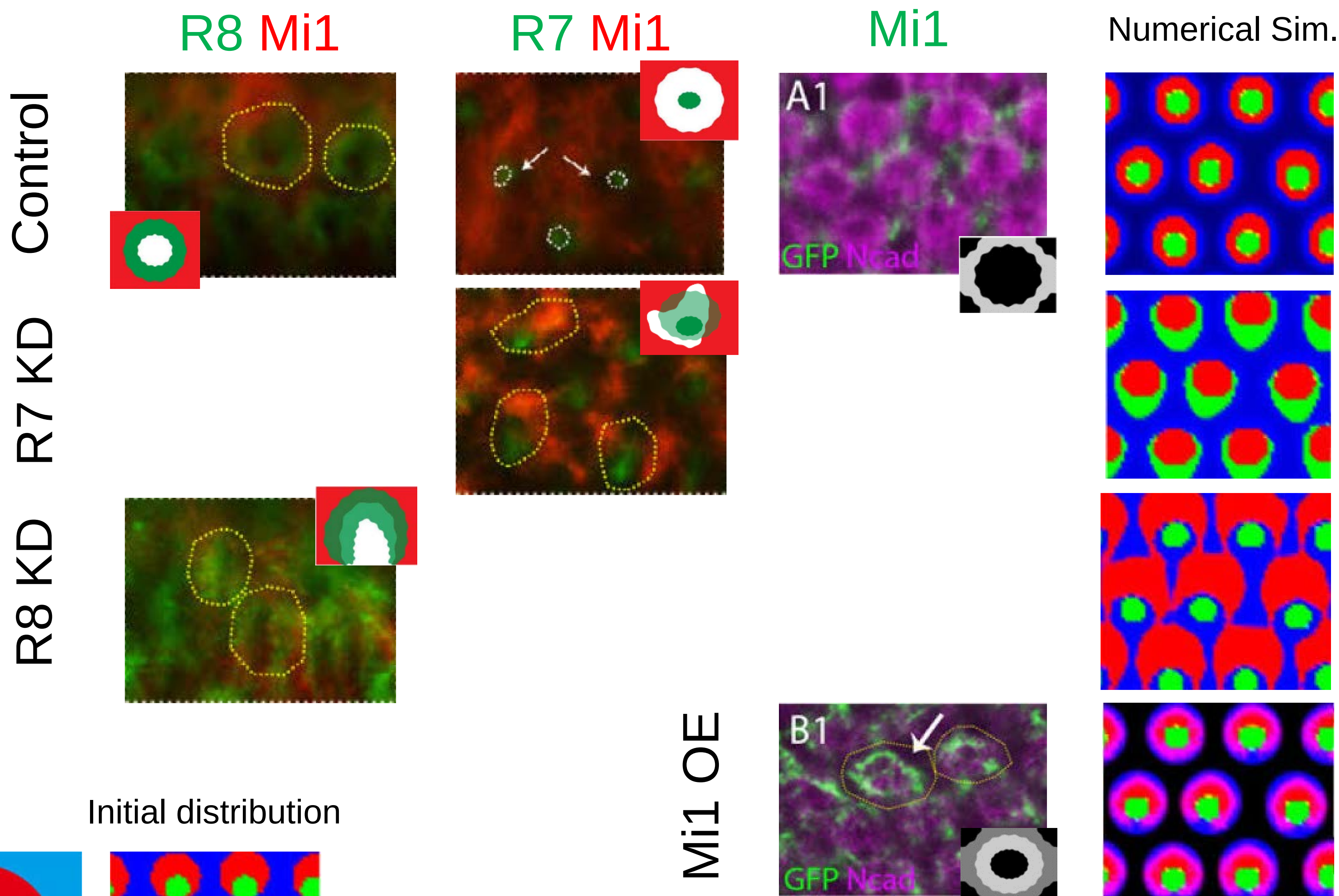


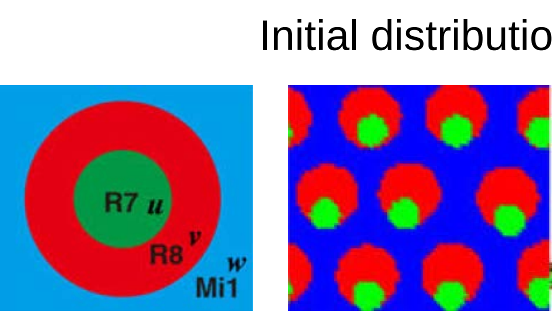
Columnar unit is a functional unit of the brain made from multiple neurons.

Developmental mechanism of column formation is unclear.

We investigated how multiple neurons are orchestrated to establish the columnar structure from the view point of differential adhesion.

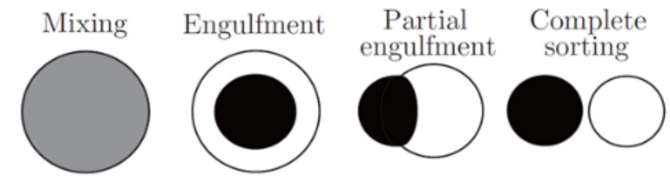
Patterns in wild and mutant type brains and NS



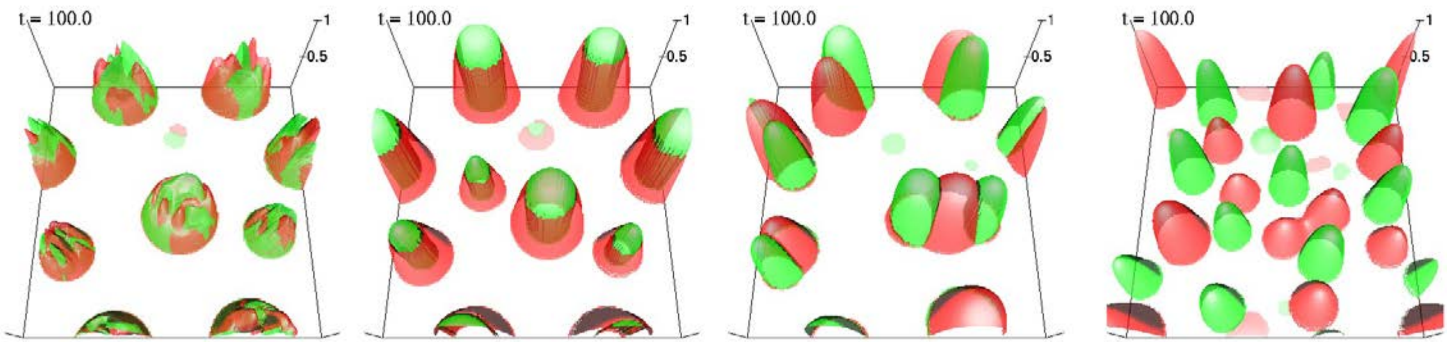


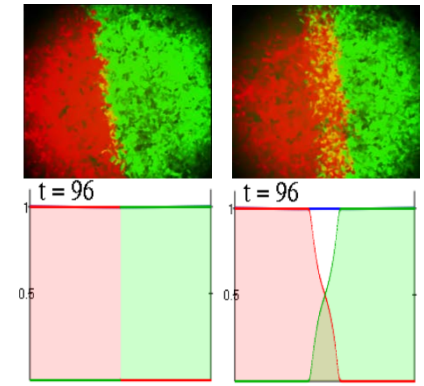
We used the mathematical model to ensure that differential adhesion could be the major driving force to establish the basic columnar structure.

Conclusion

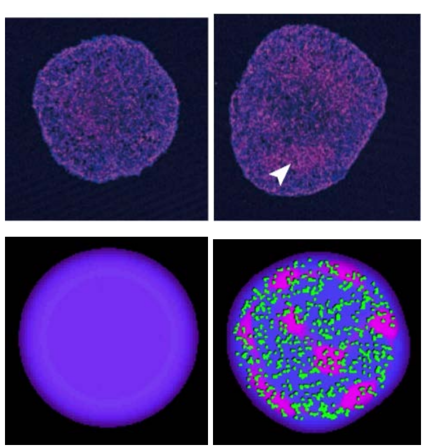


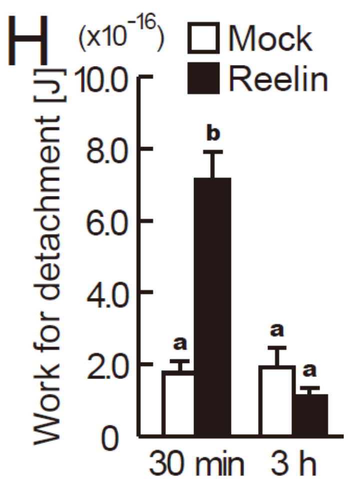
$$\begin{cases} \dfrac{\partial u}{\partial t} = \nabla \cdot (u \nabla (u+v)) - \nabla \cdot (u(1-u-v)\boldsymbol{K}_1(u,v)) + f_1(u,v), \\ \dfrac{\partial v}{\partial t} = \nabla \cdot (v \nabla (u+v)) - \nabla \cdot (v(1-u-v)\boldsymbol{K}_2(u,v)) + f_2(u,v). \end{cases}$$





Role of Reelin during Layer Formation in the Cerebral Neocortex





Role of Differential Adhesion during Columnar Unit Formation in the Drosophila brain