Modeling and simulation of multicellular and multiscale systems using the cellular Potts model

Alvaro Köhn-Luque

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University of Oslo

Monday 6 Nov
10:15 - 12:00, **Lecture**: Modelling multicellular systems using the cellular Potts model.

Tuesday 3 Nov (FV414)
10:15 - 12:00, **Hands-on 1**: Getting started with the software Morpheus.
12:15 - 14:00, **Hands-on 2**: Simulation and analysis of simple models.

1] James A Glazier and Francois Graner. Simulation of the differential adhesion driven rearrangement of biological cells. Physical Review E, 47(3):2128, 1993.
[2] Francois Graner and James A Glazier. Simulation of biological cell sort- ing using a two-dimensional extended potts model. Physical review letters, 69(13):2013, 1992.

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Joachim Mossige

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Department of Physics
University of Oslo
v402

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What is morphogenesis?

Wikipedia: From Greek *morphê (*shape) and *genesis (*creation), literally "the generation of form".

Biological process that causes a cell, tissue, organ or organism to develop its shape.

Morphogenesis is the study of how living things develop.

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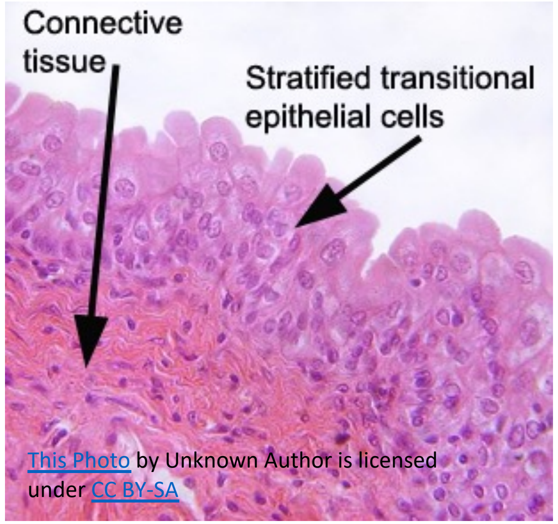

Tissue: epithelial

Organ: kidney

Gastropod shell

Organism: unicellular (e.g. bacteria) or multicellular (e.g. a dog)

Discuss: How do these tissues, organs, organisms develop into these forms?

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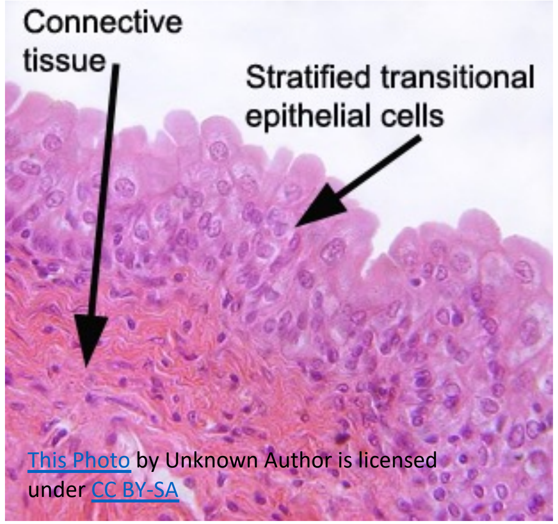

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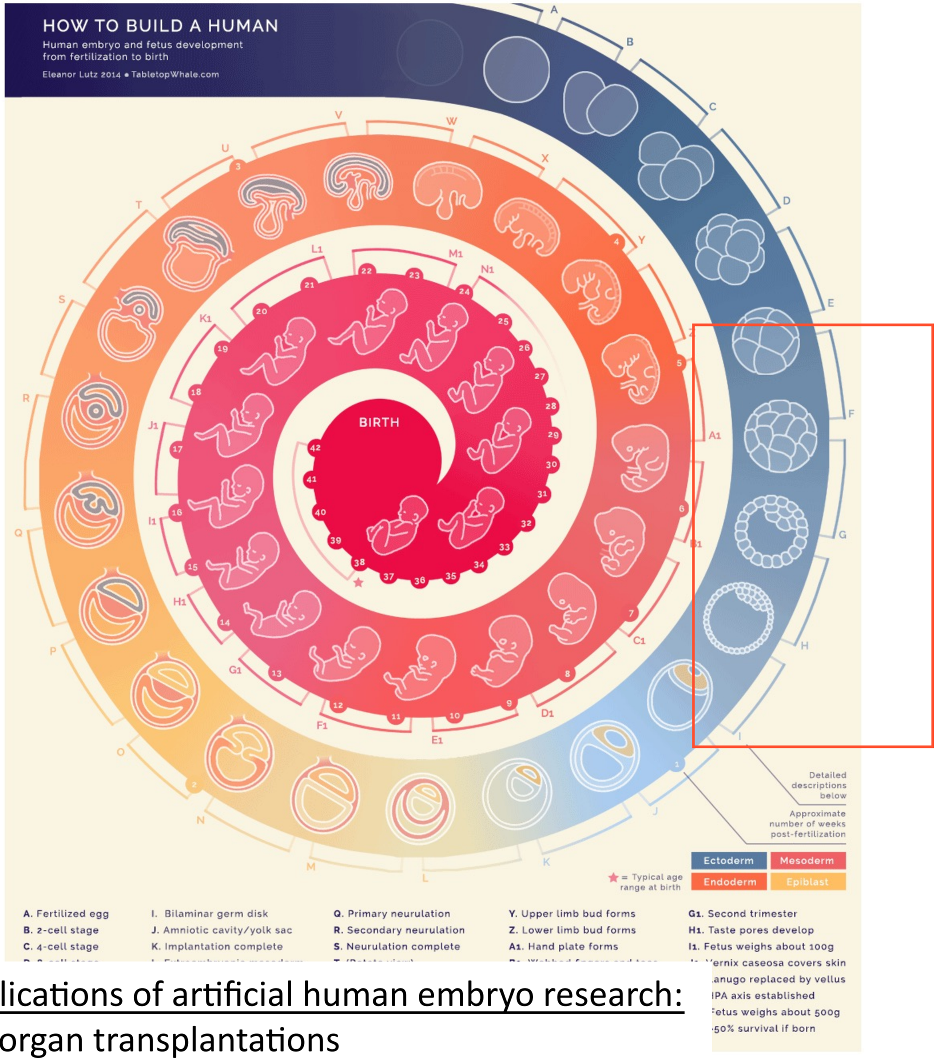
Organ: kidney

Gastropod shell

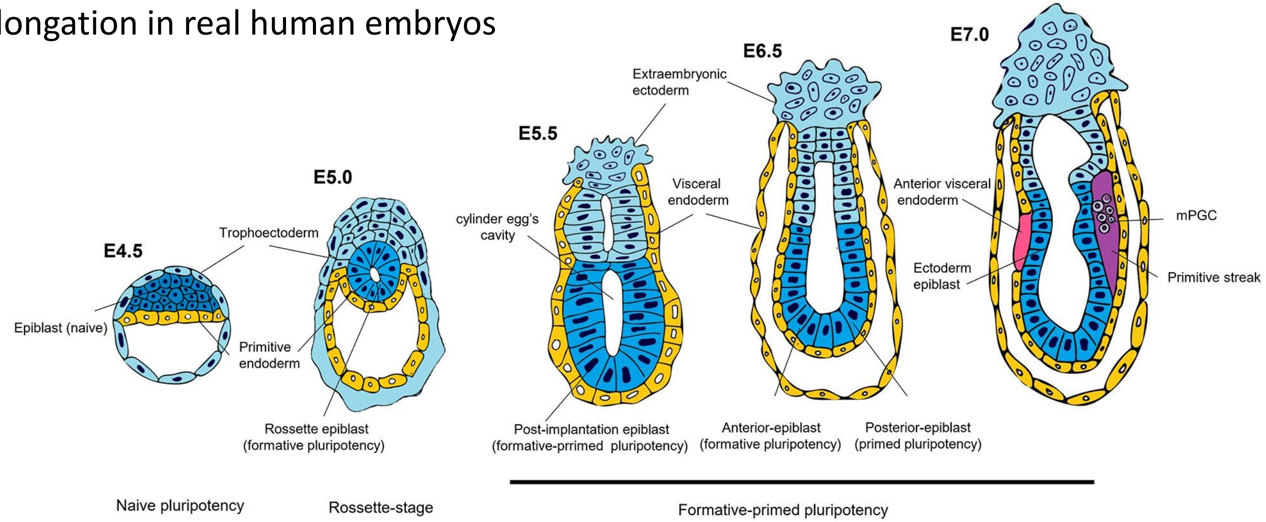
Organism: unicellular (e.g. bacteria) or multicellular (e.g. a dog)

Discuss: How do these tissues, organs, organisms develop into these forms?
Cell division, apoptosis (programmed cell death), differentiation (specialization), collective cell migration

Morphogenesis: How do human embryos develop



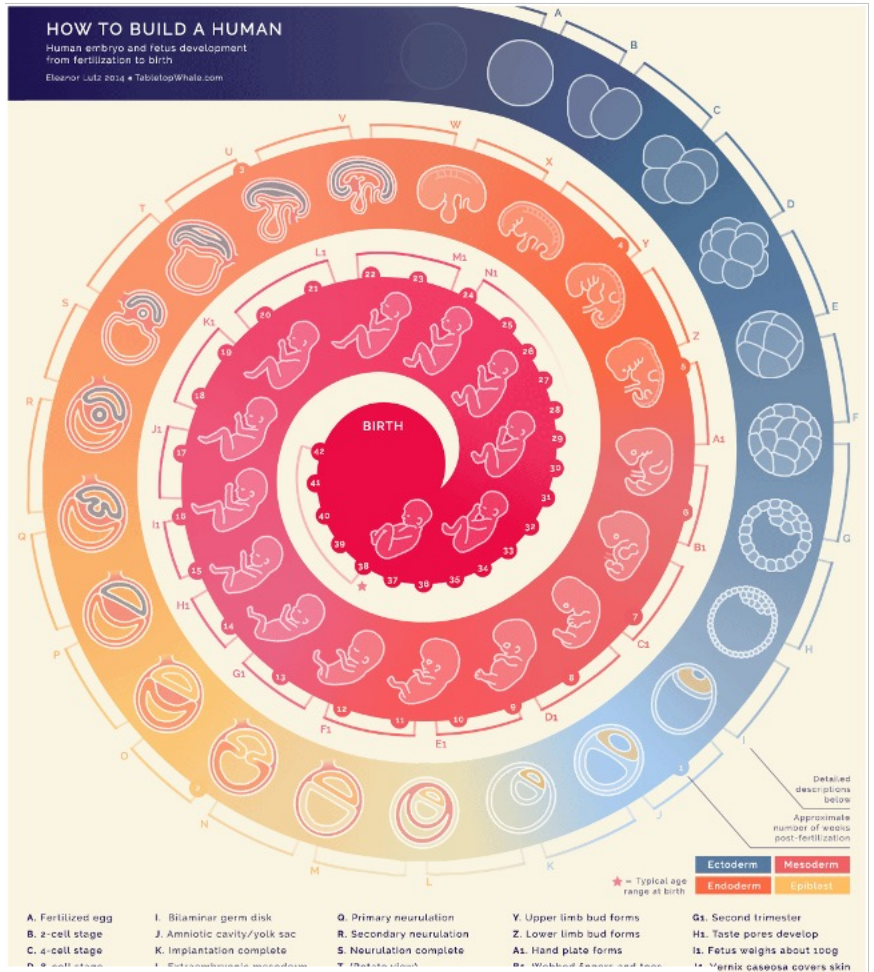
Elongation in real human embryos



<u>Applications of artificial human embryo research:</u>

- organ transplantations
- drug screening (also: toxins)
- understand early embryonic development

We can even grow (artificial)human embryos in the lab (from stem cells)



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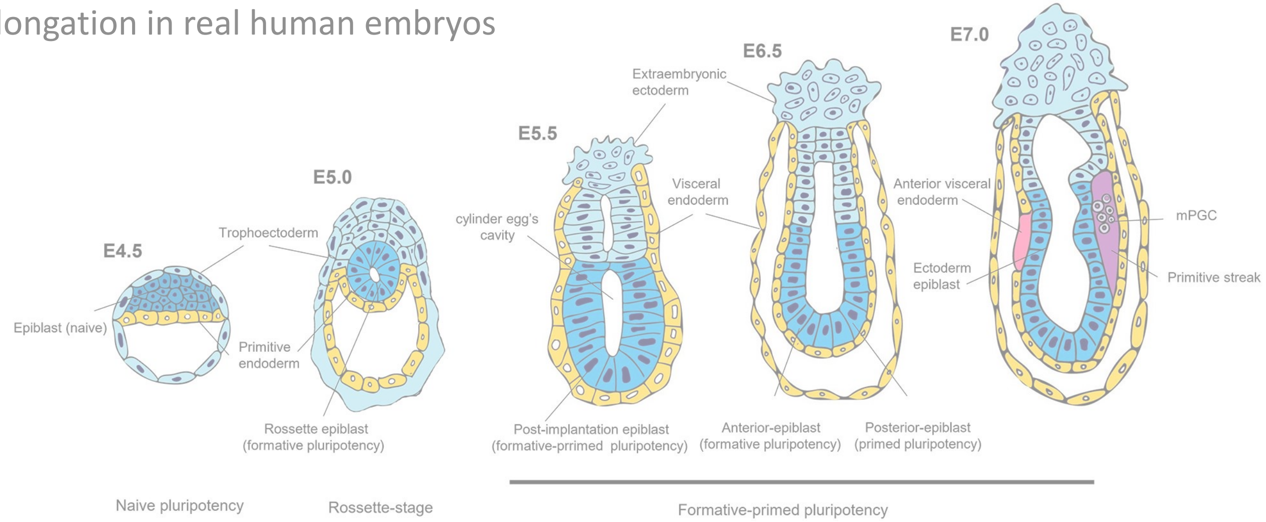
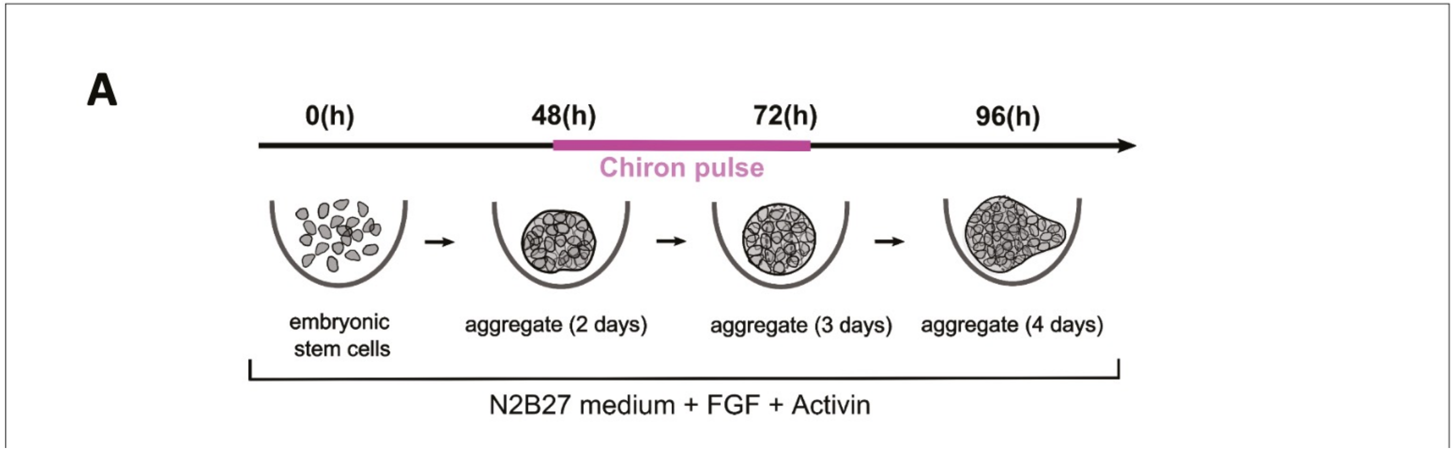


Elongation in artificial human embryos



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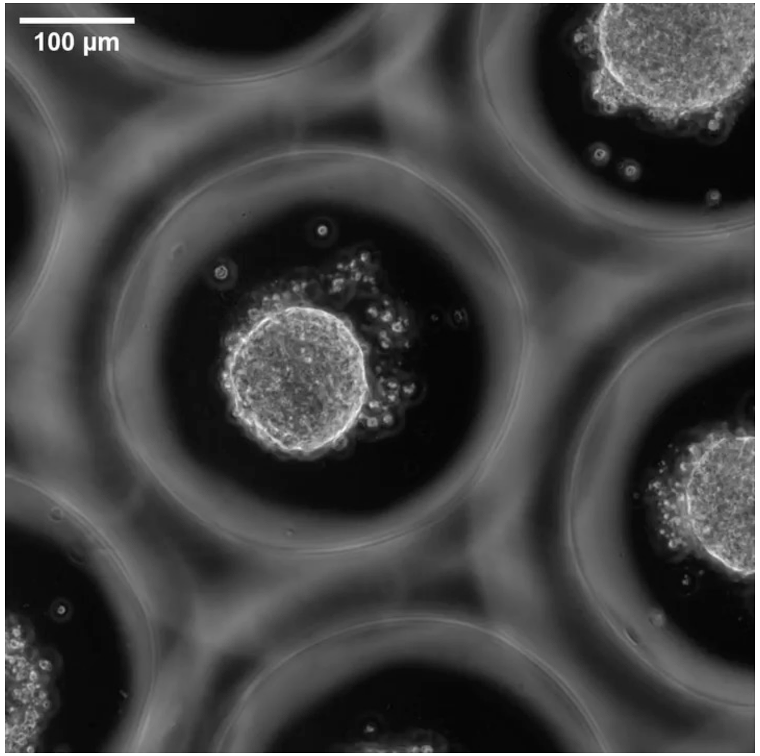
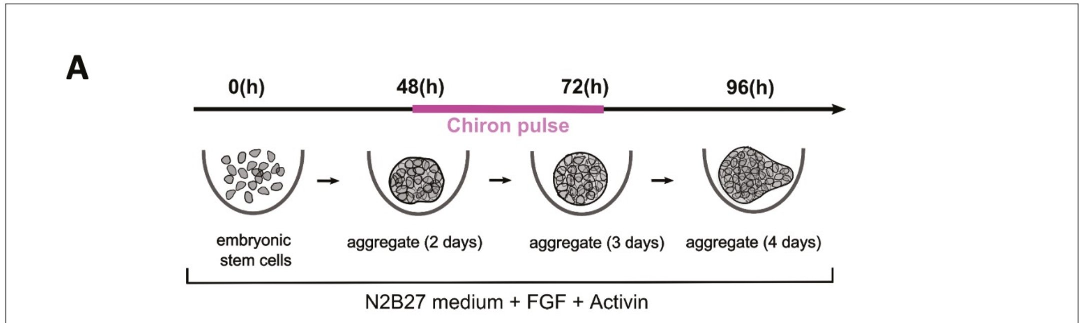
Cell flow drives elongation





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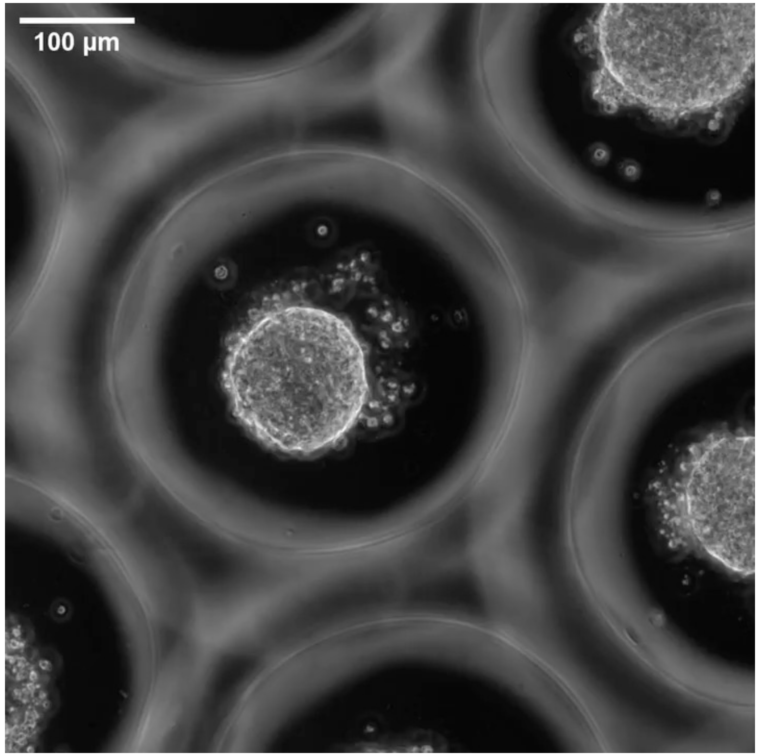

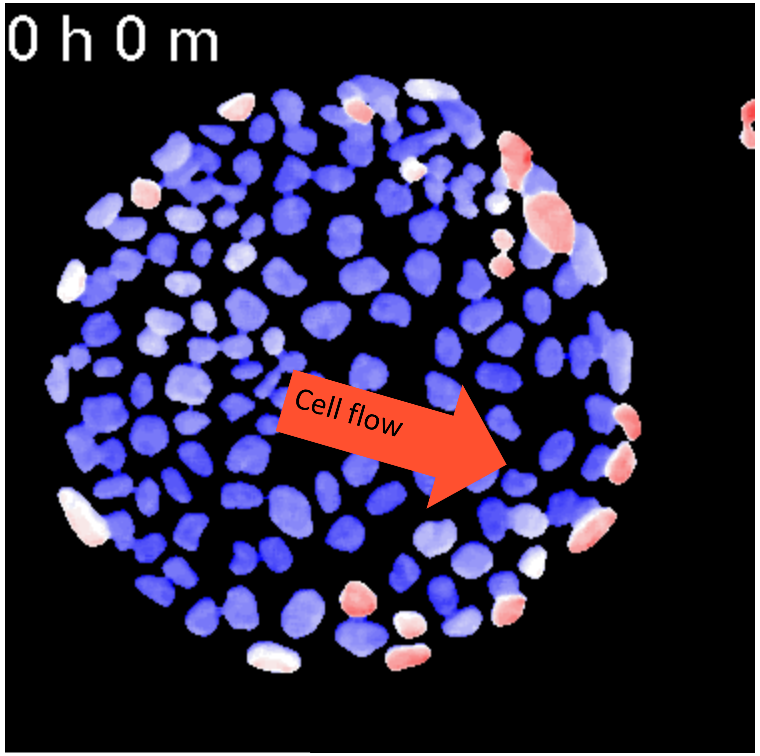

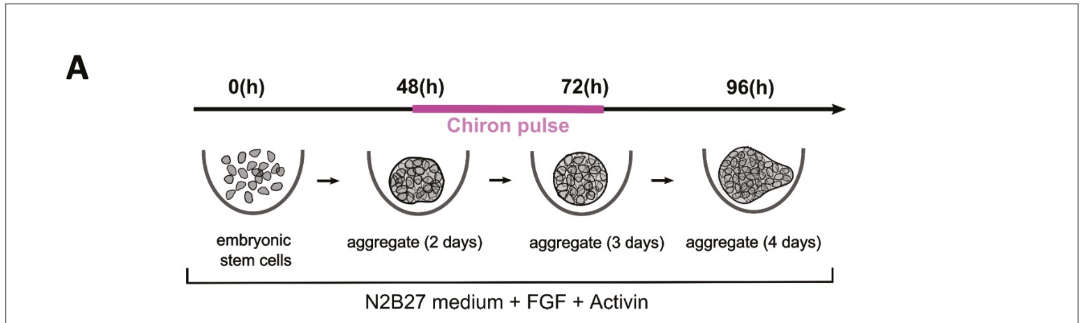

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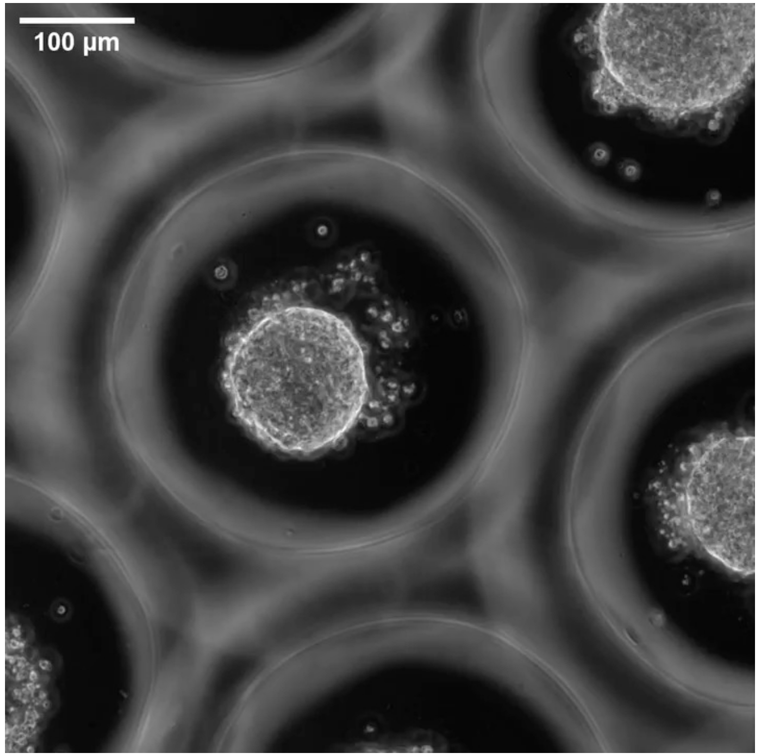
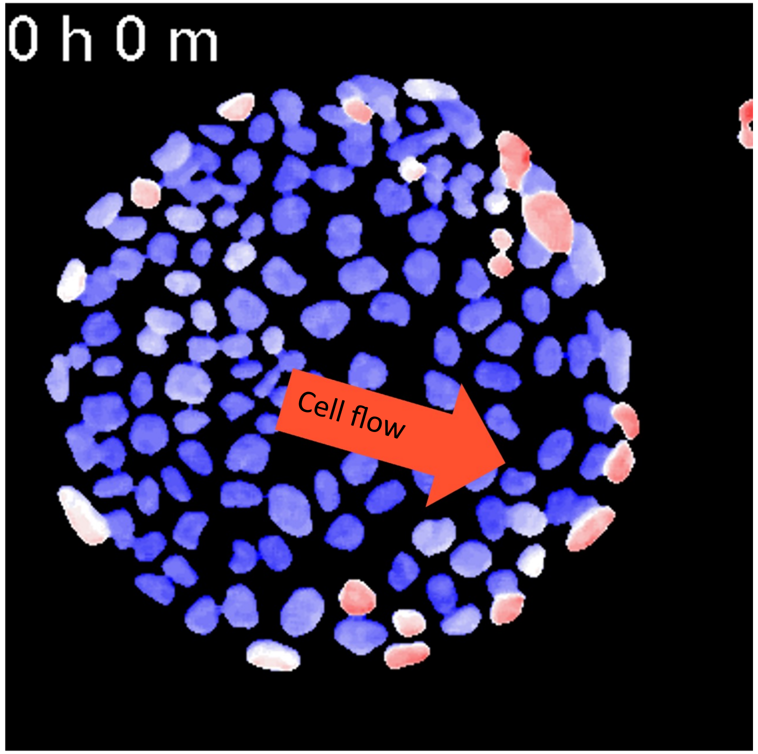
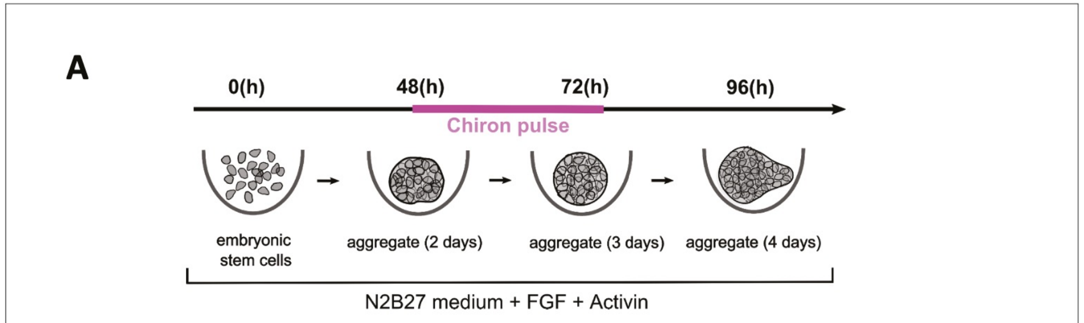




Collective motion flow in nature: Herds of sheep



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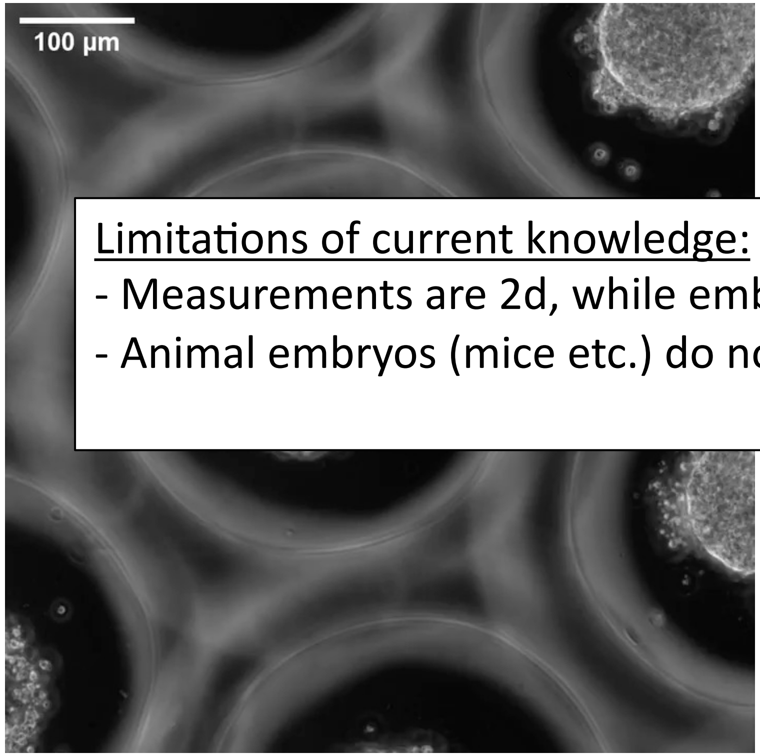

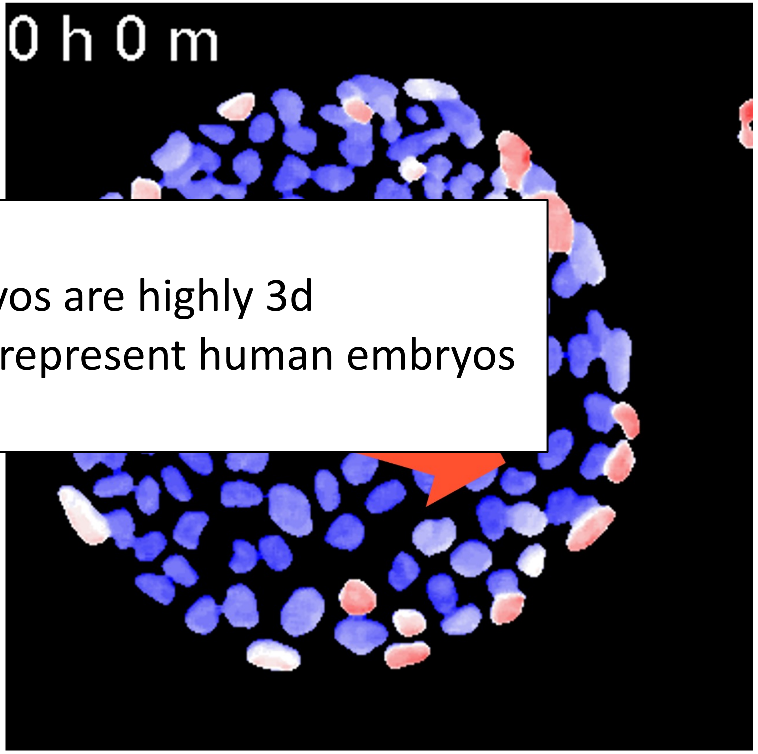

Limitations of current knowledge:

- Measurements are 2d, while embryos are highly 3d
- Animal embryos (mice etc.) do not represent human embryos

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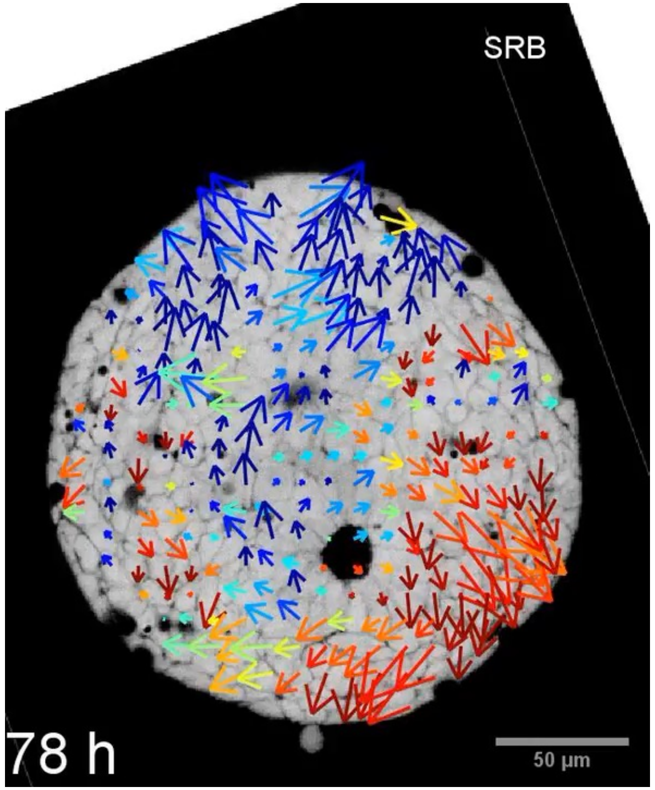
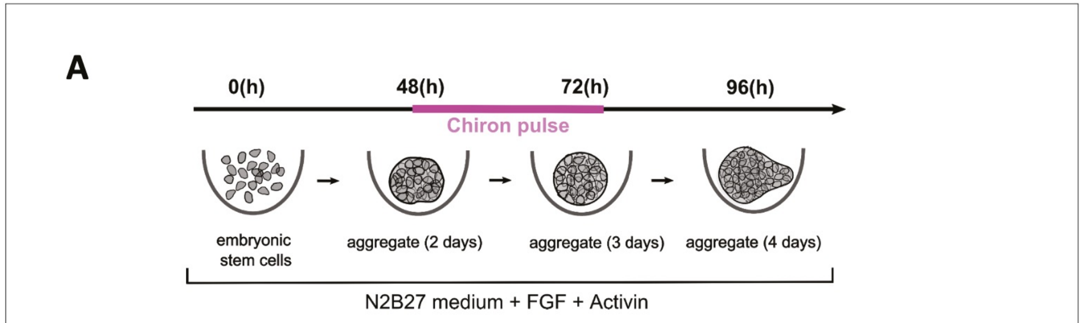


Motion capture of cells: Flow field



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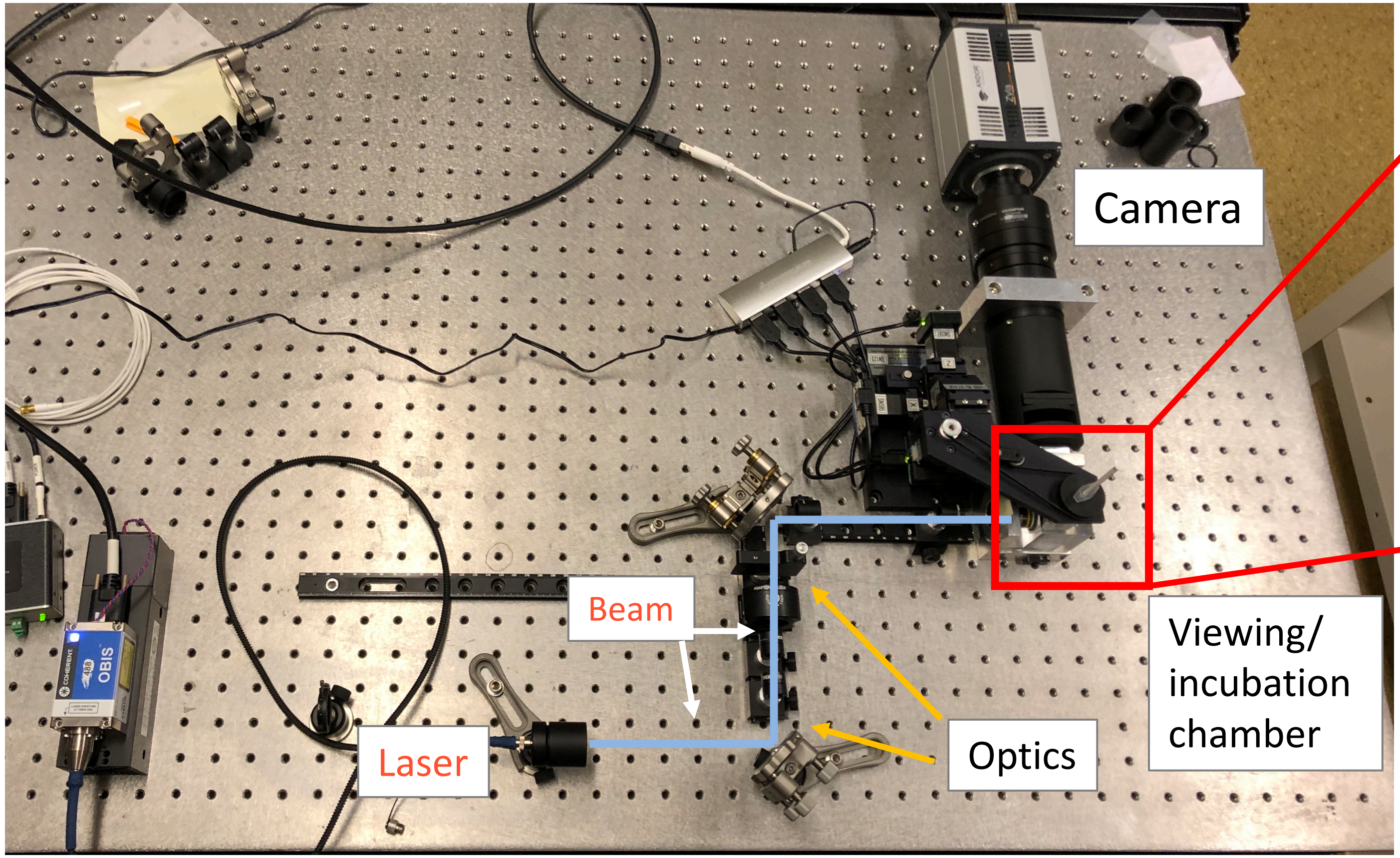
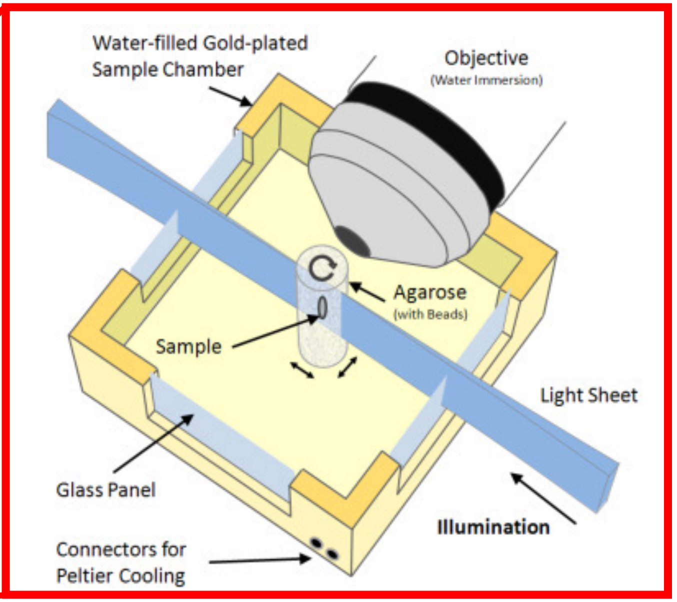
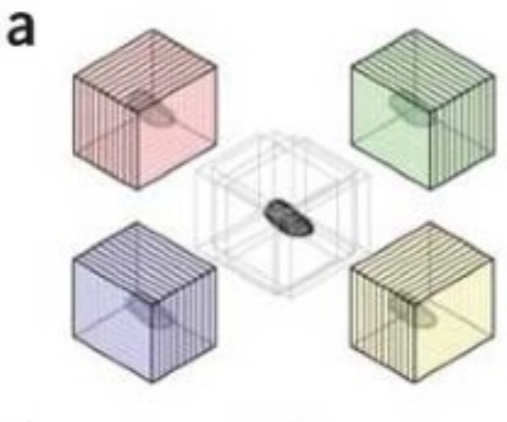
We built a light sheet microscope to visualize 3d motion of cells and how embryos grow



Our light sheet microscope





Top image from openspim.org. Bottom image: Preibisch, S., Saalfeld, S., Schindelin, J., & Tomancak, P. (2010). Software for bead-based registration of selective plane illumination microscopy data. *Nature methods*, *7*(6), 418-419.

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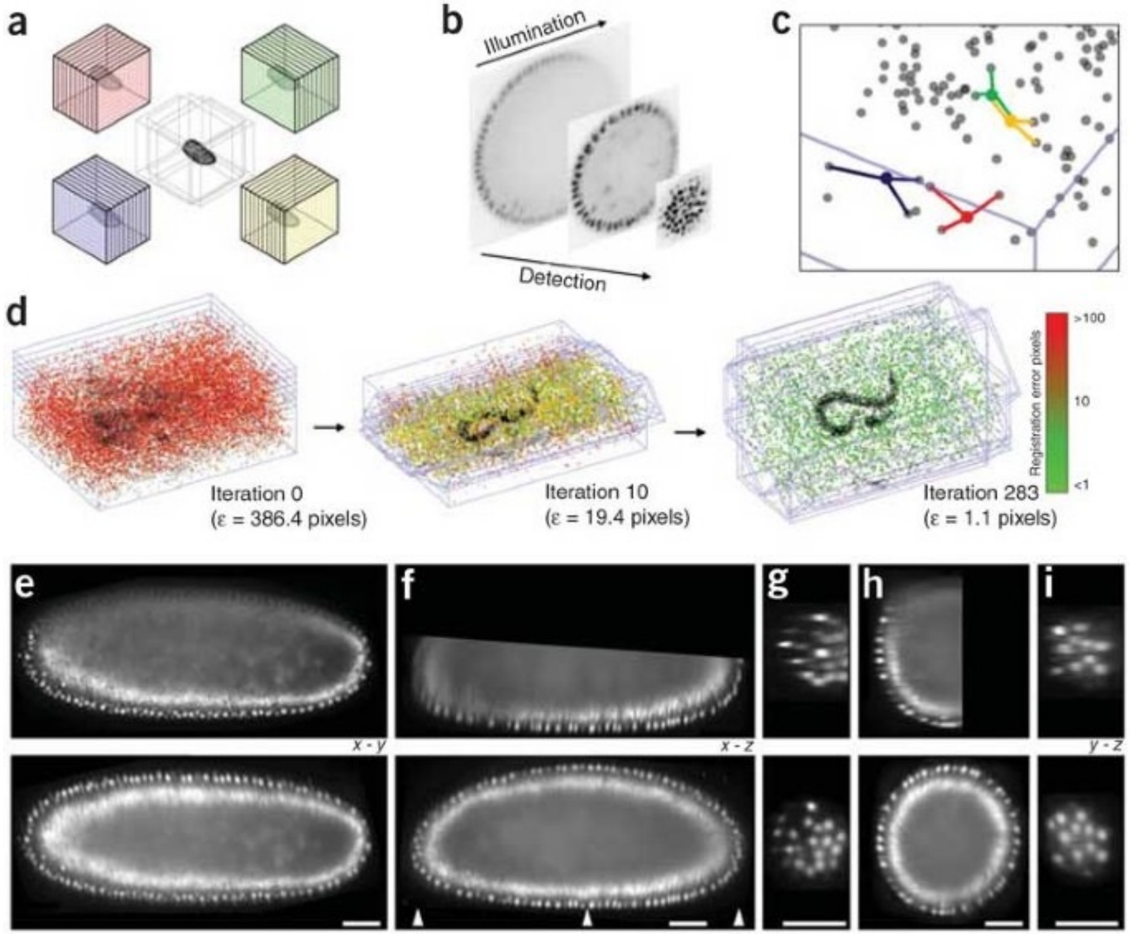
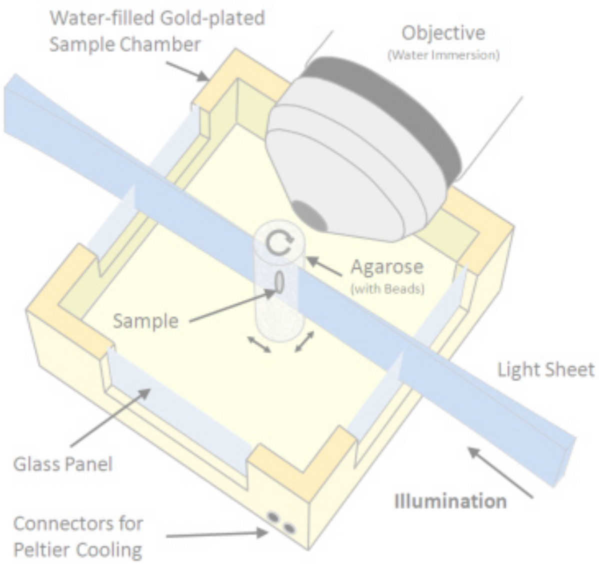
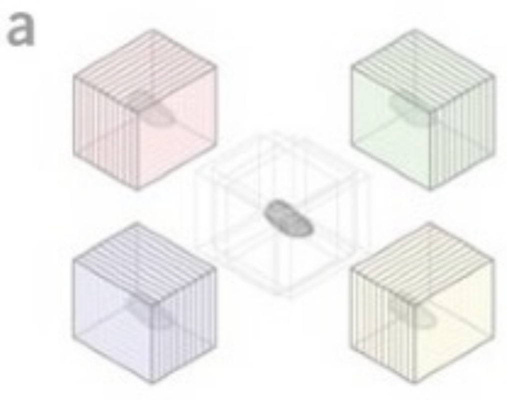


Visualization of fruit fly embryo development





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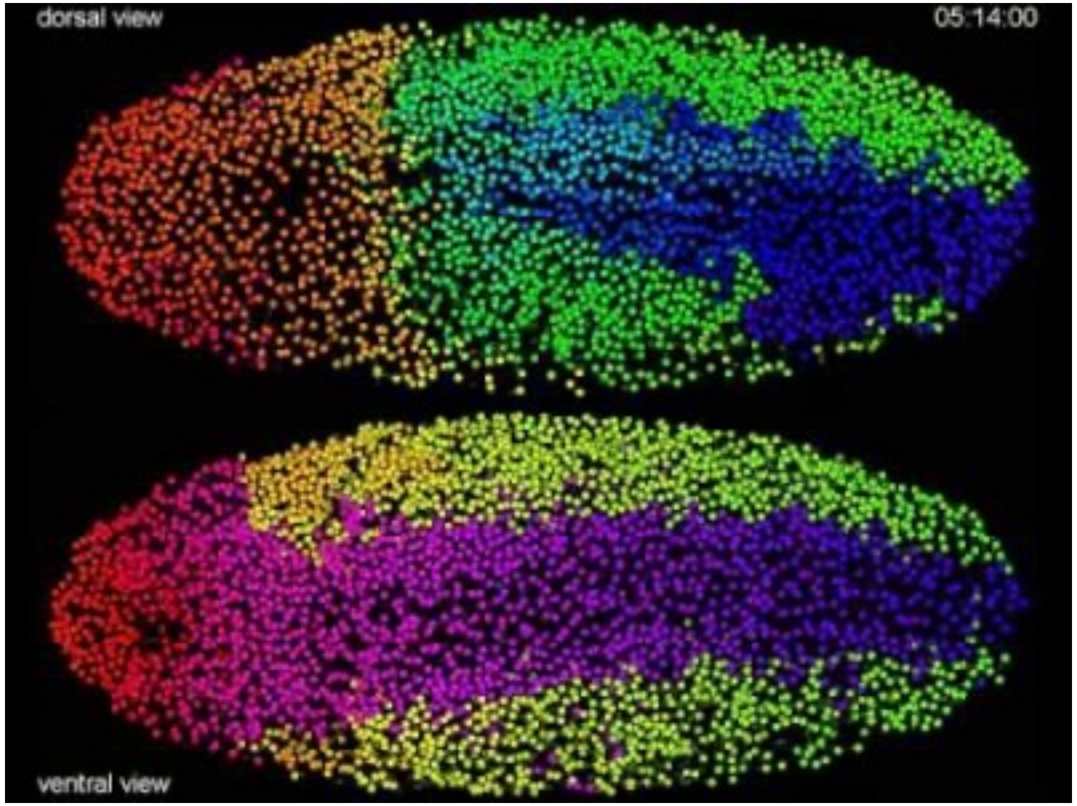
What SPIM can do: Fruit fly (Drosophila) embryogenesis



“Digital fruit fly embryo” obtained with light-sheet microscopy
Source: https://www.youtube.com/watch?v=QU4YXD9GxFo
Credit: Kristin Branson, Fernando Amat, Bill Lemon and Philipp Keller (HHMI/Janelia)

Acknowledgements

LIVSVITENSKAP
LIFE SCIENCE

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Centre director at RITMO

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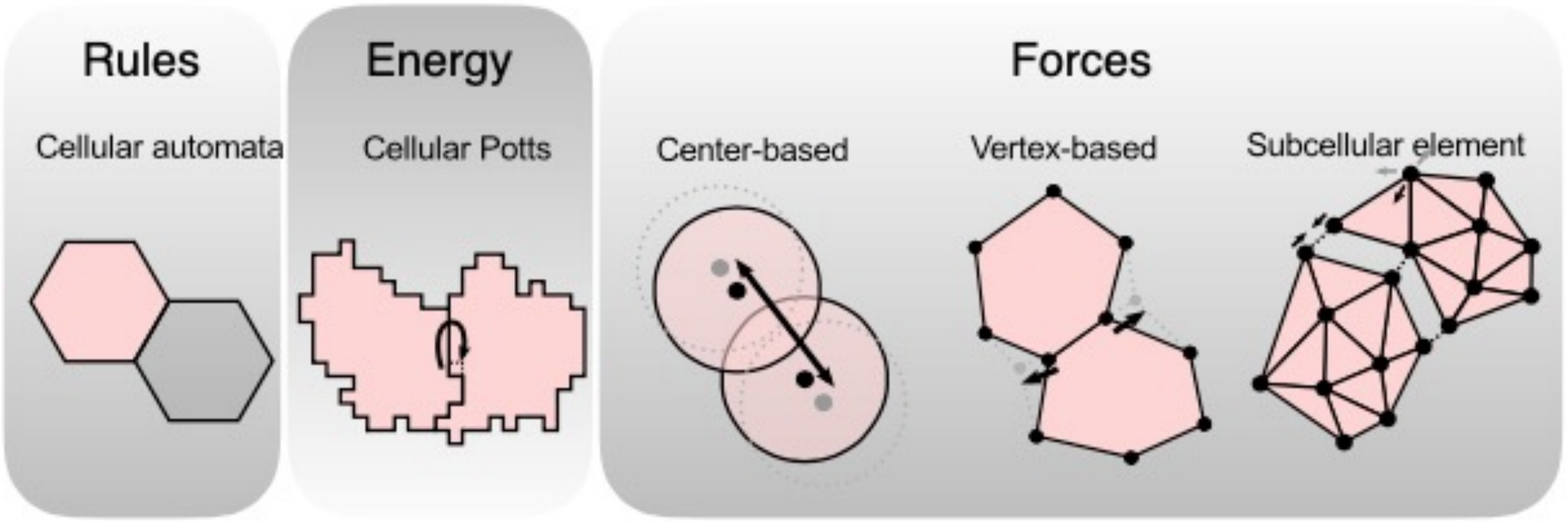
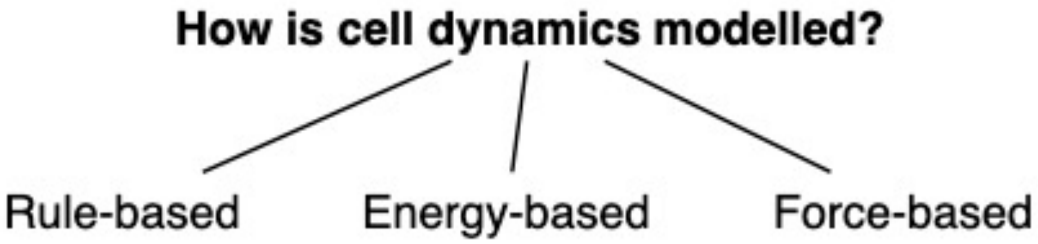
Håkon Høgset, postdoc at HTH

Luiza Agheluta-Bauer, Dept. Phys

Dongho Kwak, buddy and
soon-to-be PhD at RITMO

Different cell-based modeling approaches



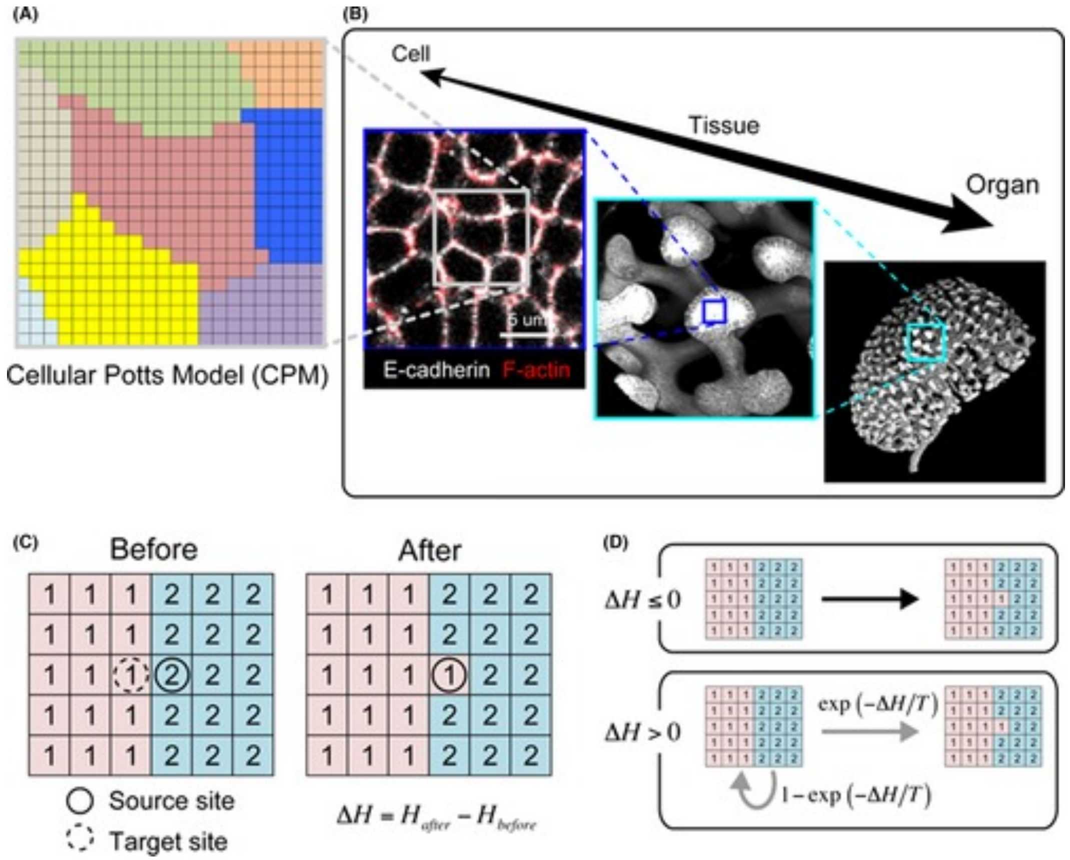


Cellular Potts Model (CPM): Capabilities

- Energy based: Physically sound
  - Minimizes the energy of each cell in each time step
  - Interaction with cell surroundings
    - other cells, ECM, or substrate
  - Volume changes:
    - Cell growth or shrinkage (apoptosis)

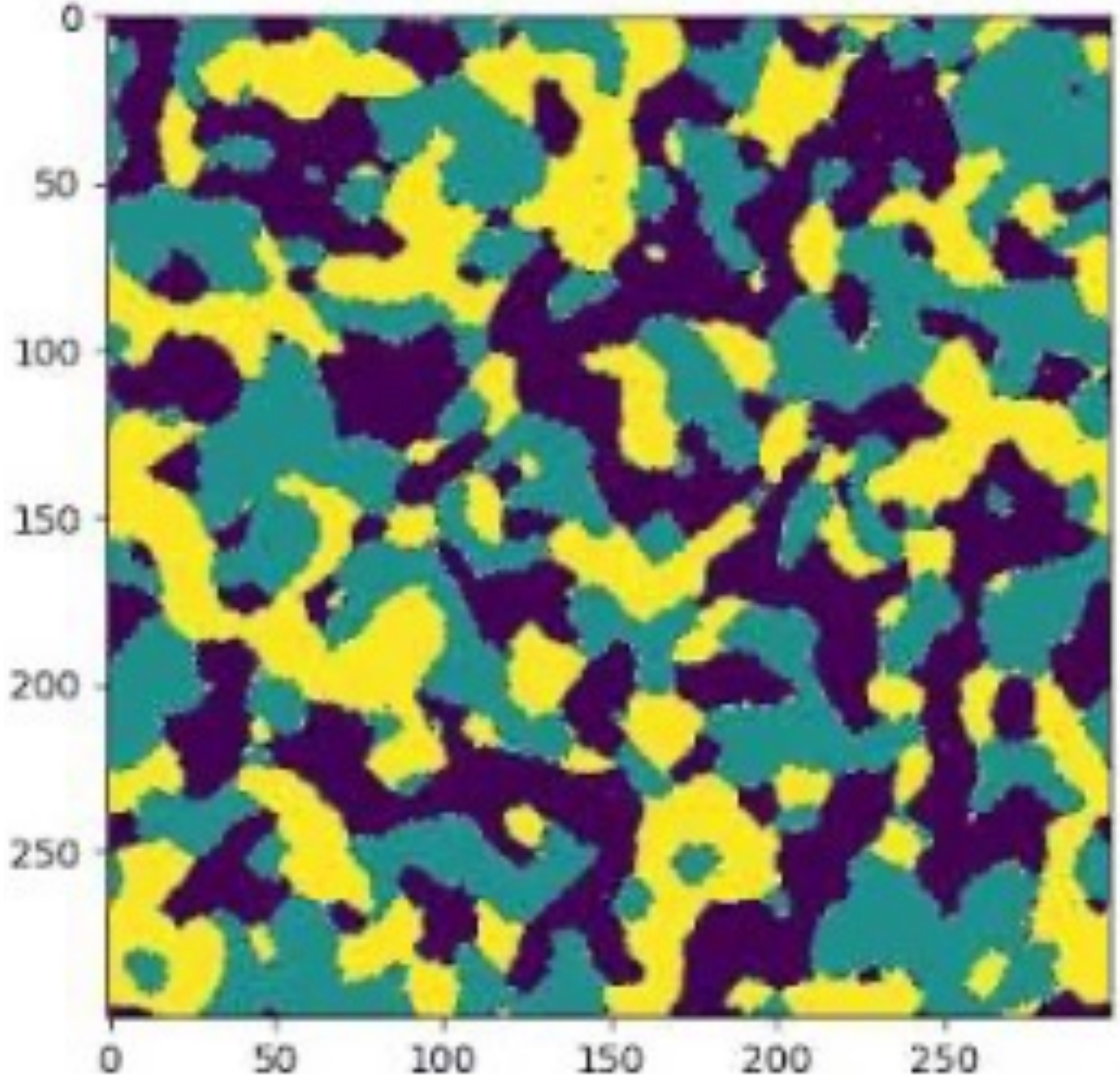
- Easy to implement
  - We will use Morpheus (no coding)

- Capabilities:
  - Cell sorting (Computer lab exercise)
  - Pattern formation
  - Tumor growth (Computer lab exercise)
  - Morphogenesis
  - Wound healing
  - Model response to a chemical gradient
  - Model response to forces



Hirashima, T., Rens, E. G., & Merks, R. M. (2017). Cellular Potts modeling of complex multicellular behaviors in tissue morphogenesis. *Development, growth & differentiation*, *59*(5), 329-339.

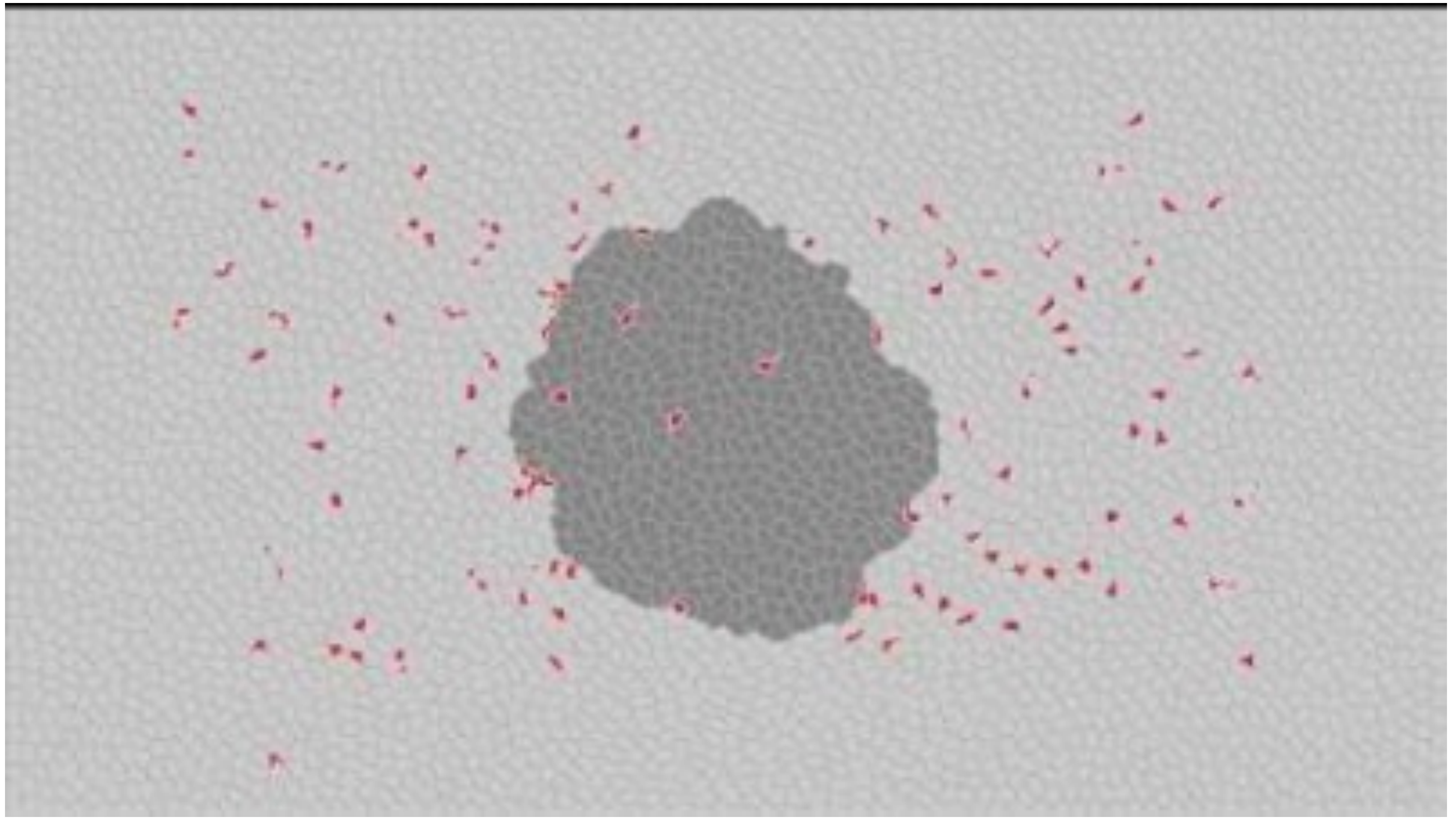
What CPM can do: Cell sorting



https://www.youtube.com/watch?v=kz_R32hVRpc
Code: http://crackeconcept.blogspot.com/2020/07/potts-model-simulation-code-python.html

What CPM can do: Tumor growth

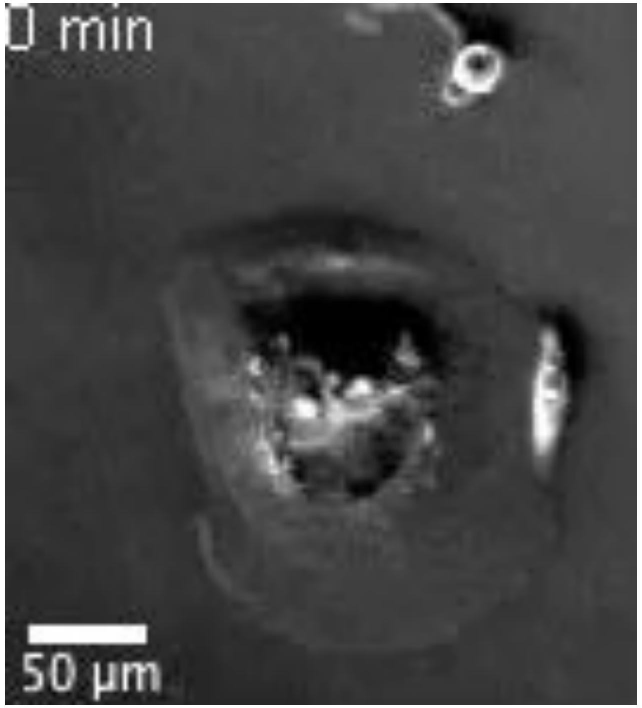
- Growing tumor (dark grey) in stromal tissue (light grey)
- T cells (red) are infiltrating the growing tumor.
- Note: tumor cell division is accelerated in this simulation for visualization purposes and occurs much faster than in a realistic setting.

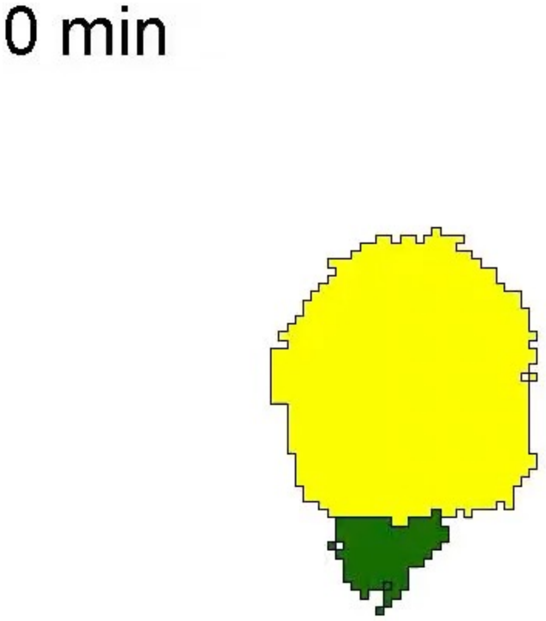


Niculescu, I., Textor, J., & De Boer, R. J. (2015). Crawling and gliding: a computational model for shape-driven cell migration. *PLoS computational biology*, *11*(10), e1004280.
Source code: https://github.com/ingewortel/artistoo

What CPM can do: Study how senescent cells* affects the movement of active cells

- *Cells that stop growing and successively expands
- Combining experiments with simulations
- Finding: The adhesion between normal (MDA-MB-231) cells and senescent cells is much weaker than the adhesion between normal cells.
- The distance traveled by normal cells along senescent cells is much longer than the distance traveled along other normal cells.
- Proposed explanation: Expansion of the senescent cell membrane could decrease the number of cell adhesion molecules per area.



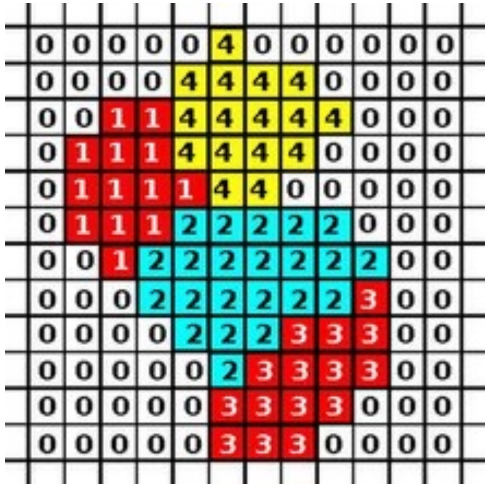


Gabuardi, T. L., Lee, H. G., & Lee, K. J. (2022). Role of senescent cells in the motile behavior of active, non-senescent cells in confluent populations. *Scientific reports*, *12*(1), 3857.

Cellular Potts Model (CPM): How it works ☺

- Cells (or groups of cells) are represented as deformable objects on a lattice
- Each cell occupies one lattice site or several sites
- The energy H of a cell results from adhesion with neighbors
  - Adhesion with different cell types (1,2,3,4)
  - Adhesion with ECM or medium (0)

+ the resistance to volume changes



Lattice used in CPM. From Wikipedia

- During CPM simulation, the **energy function** H is minimized in each time step

$$H = \sum_{i,j \text{ neighbors}} J\left(\tau(\sigma_i), \tau(\sigma_j)\right)\left(1 - \delta(\sigma_i, \sigma_j)\right) + \lambda \sum_{\sigma_i} \left(v(\sigma_i) - V(\sigma_i)\right)^2,$$

Adhesion with neighbors (surface energy)

Resistance to volume changes (Volume energy)

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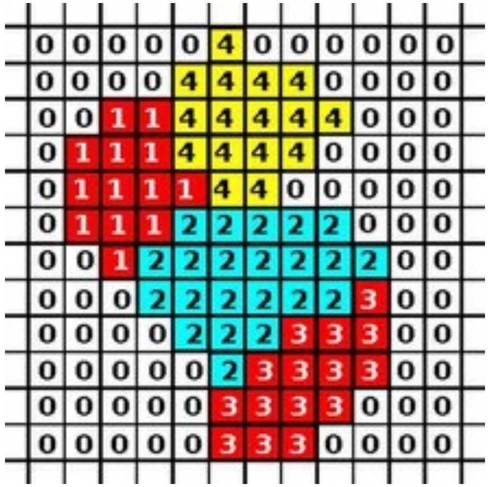
\+ the resistance to volume changes (neglect in this lecture)



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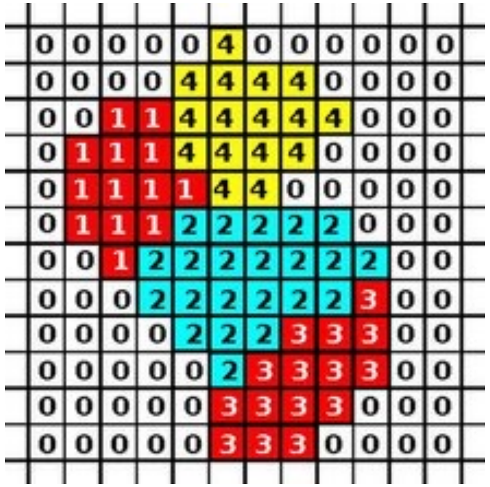
Energy function: What the terms mean

- Cell index: σ
- Cell type: $\tau(\sigma)$
- Surface energy between a randomly picked cell and a neighbor: J
- lattice sites: i, j



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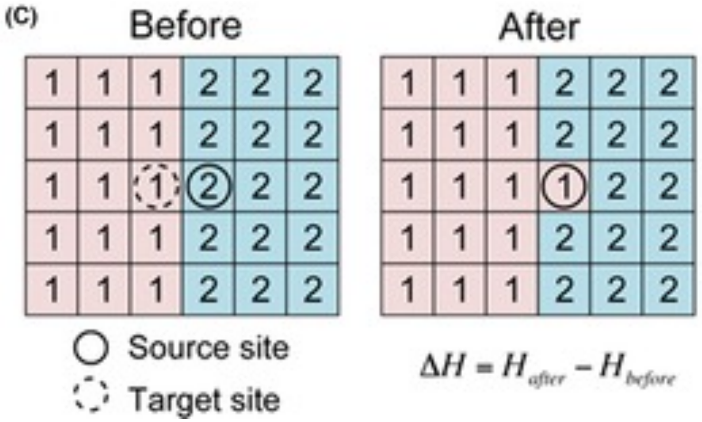
CPM algorithm: What is the probability that a cell moves from one lattice site to the next?

1. Choose a random (source) site, i ○
   - $\tau = 2$



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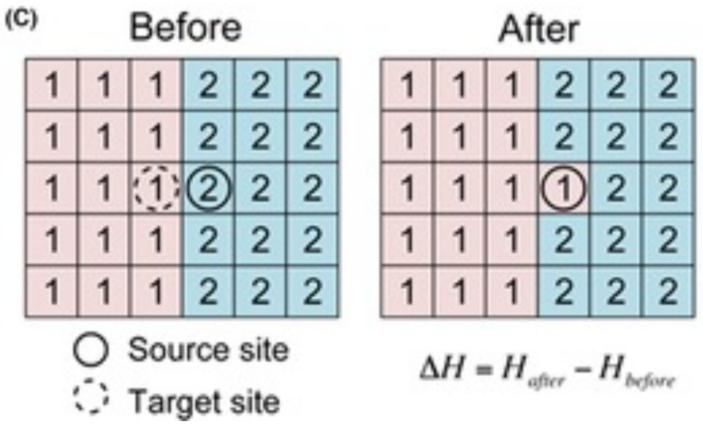

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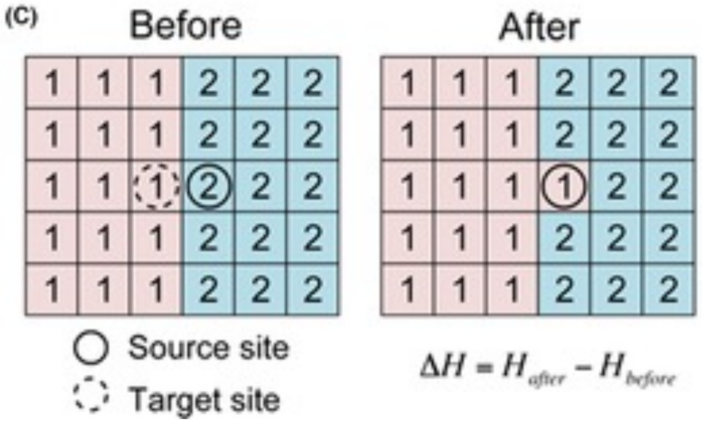

$$\Delta H = H_{after} - H_{before}$$

associated with copying the target site index (with index 1) onto the source site (with index 2)

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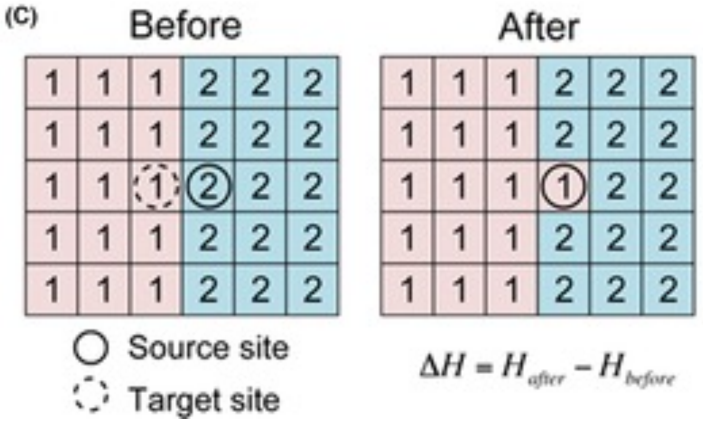

$$\Delta \mathrm{H} = \mathrm{H}_{after} - H_{before}$$

associated with copying the target site index (with index 1) onto the source site (with index 2)

If the energy cost is negative or zero, $\Delta H \leq 0$: always accept the copy

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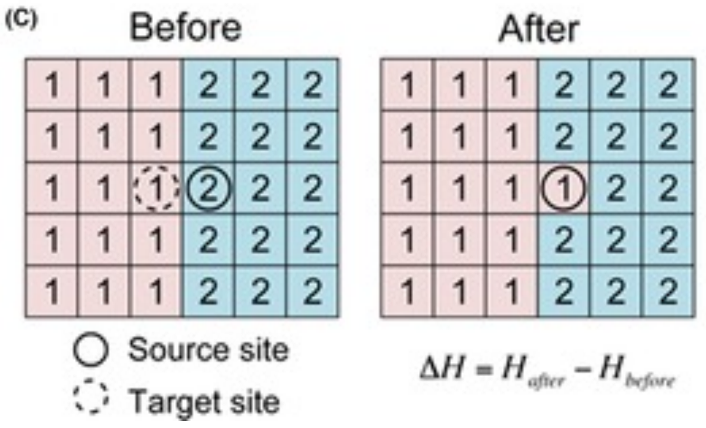
$$H = \sum_{i,j \text{ neighbors}} J\left(\tau(\sigma_i), \tau(\sigma_j)\right)\left(1 - \delta(\sigma_i, \sigma_j)\right) + \lambda \sum_{\sigma_i} \left(v(\sigma_i) - V(\sigma_i)\right)^2,$$

Adhesion with neighbors

Resistance to volume changes

CPM algorithm: What is the probability that a cell moves from one lattice site to the next?

1. Choose a random (source) site, i ○
   - $\tau = 2$
2. Choose a neighbor (target) site, j ◌
   - $\tau = 1$
3. Calculate the difference in energy



$$\Delta \mathrm{H} = \mathrm{H}_{after} - H_{before}$$

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If the energy cost is negative or zero, $\Delta H \leq 0$: always accept the copy

If the energy cost positive, $\Delta H > 0$:

accept the copy with probability $\mathrm{P}\,(\Delta\, H, \mathrm{T}) = e^{-\Delta H / T}$

Energy minimization function

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Adhesion with neighbors

Resistance to volume changes

Exercise! What's the probability that this copy attempt is accepted? What is ΔH?

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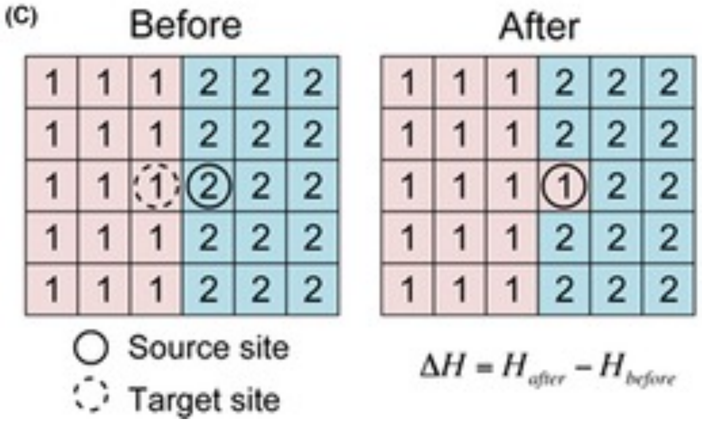

$$\Delta H = H_{after} - H_{before}$$

<u>Adhesion energy J between</u>

- cell type 1 and 2 is 2α, i.e. $J(\tau_1, \tau_2) = J(\tau_1, \tau_2) = 2\alpha$
- cell type 1 with itself is α, i.e. $J(\tau_1, \tau_1) = \alpha$
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Adhesion with neighbors

Resistance to volume changes

Solution: The copy is accepted with probability $\mathrm{P}\,(\Delta H, \mathrm{T}) = e^{-2\alpha/T}$

1. Energy $H_{before} = 3 \cdot \alpha + 2\alpha = 5\alpha$
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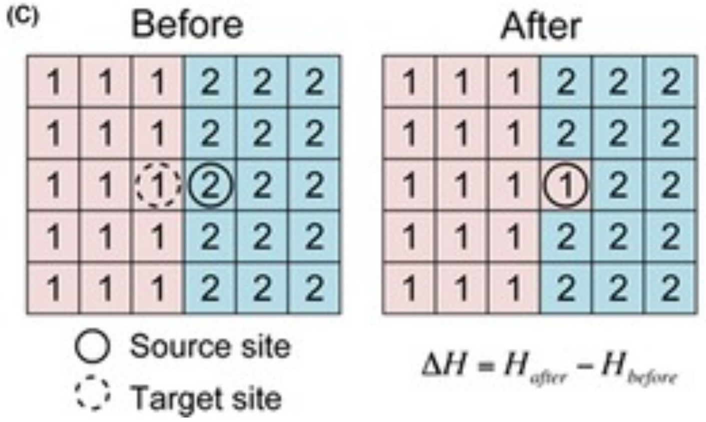

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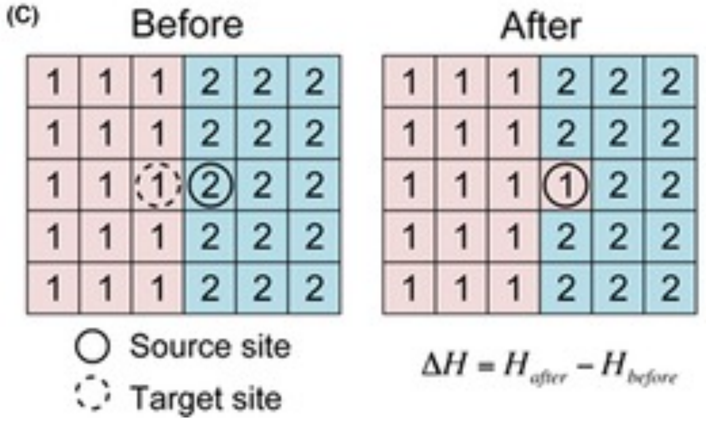

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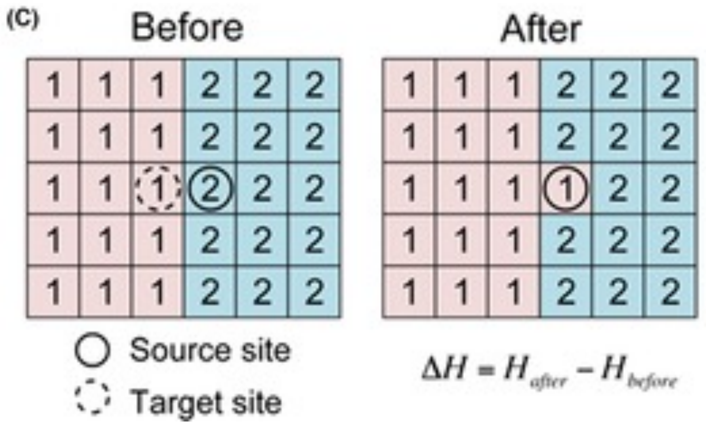

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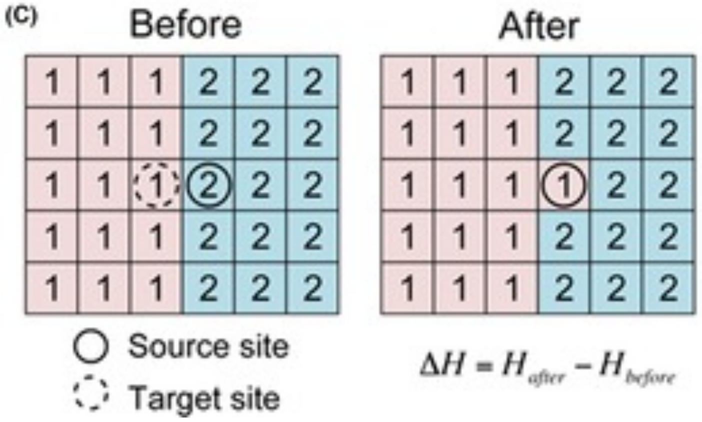
Adhesion with neighbors

Resistance to volume changes

Discussion: What happens when T goes to 1) infinity and 2) zero



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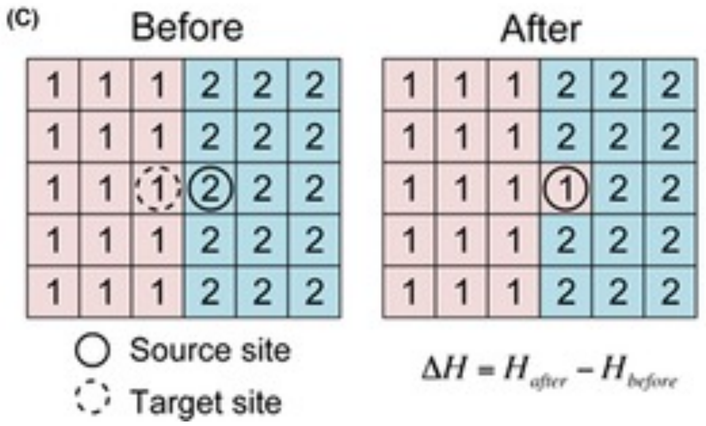

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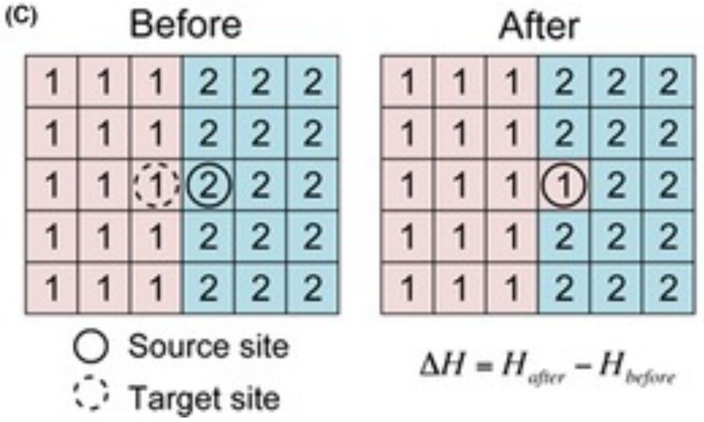
Adhesion with neighbors

Resistance to volume changes

Discussion: What happens when T goes to 1) infinity and 2) zero



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8. What does this mean?
9. This means that when we increase the Boltzmann temperature, T, it is more likely that cells move to new positions even if this is energetically unfavorable

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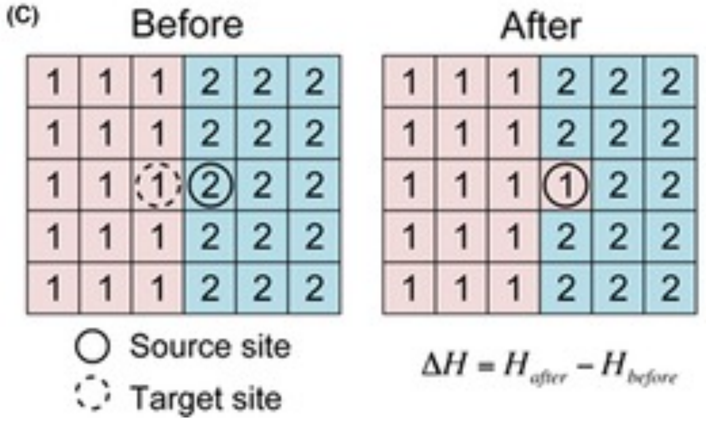
Adhesion with neighbors

Resistance to volume changes

Exercise! Plot P (y-axis) vs. ΔH (x-axis; $-2 < \Delta H < 10$) for different T-values (0, 2, 5, 100)

$$P(\Delta H, T) = exp(-\Delta H / T)$$



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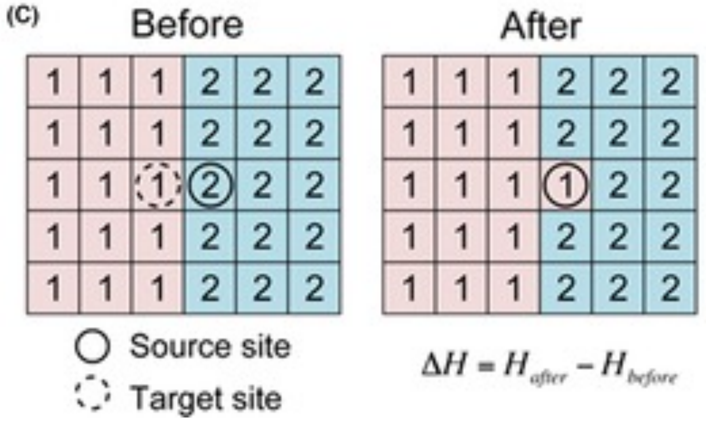
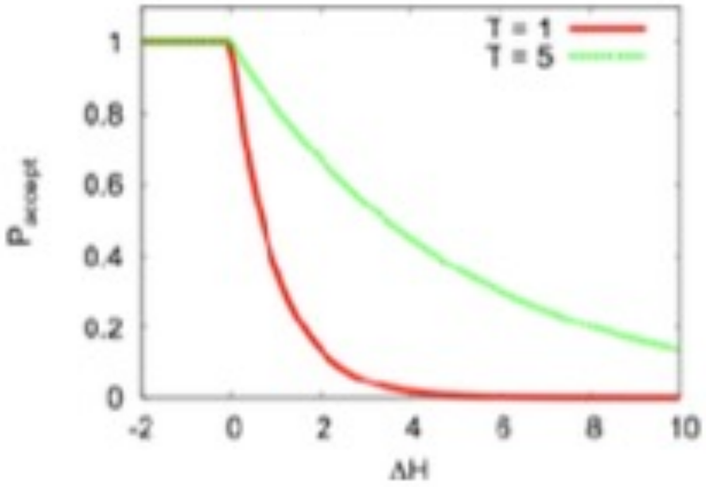


- Probabillty to accept copy depends on ΔH:

$$P(\Delta H) = \begin{cases} 1 & \text{if } \Delta H \leq 0 \\ e^{-\frac{\Delta H}{T}} & \text{otherwise} \end{cases}$$



- if the cost is negative, always accept the copy
- The probability that the copy will be accepted increases with T
- T is the Boltzmann temperature, not physical temperature

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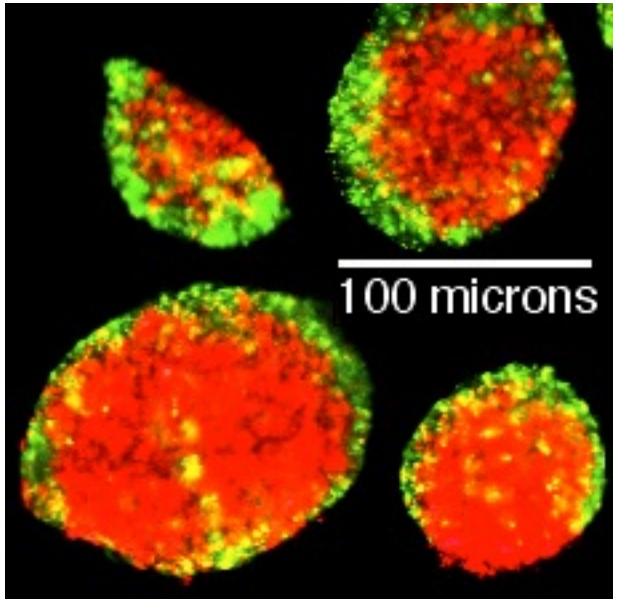
Adhesion with neighbors

Resistance to volume changes

Special case 1: Cell sorting

- Cells with a lower J value for their membrane are more likely to stick together than cells with a higher J value

=> Simulate different sorting patterns by varying the J value



Morphogenesis. (2023, October 25).
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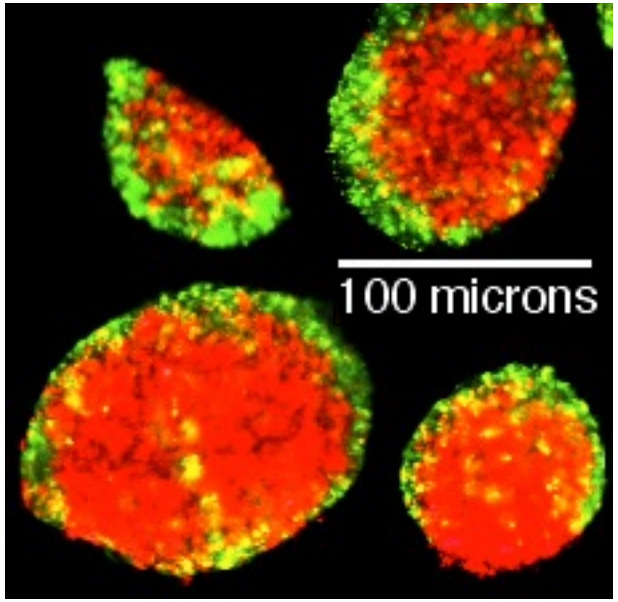

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to determine whether contact energies favor homotypic ($\gamma_{\tau_1,\tau_2} > 0$) or heterotypic ($\gamma_{\tau_1,\tau_2} < 0$) cell bonds.

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Adhesion with neighbors

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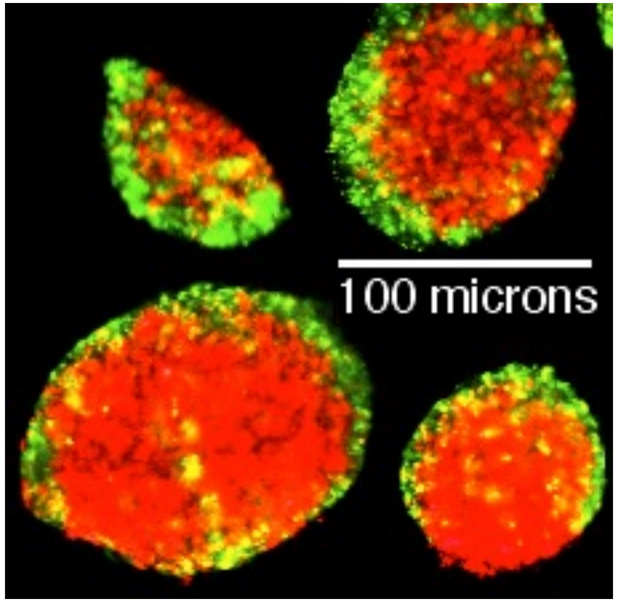
Exercise! Cell sorting



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Define: *m* for medium, *y* for yellow and *r* for red cells.

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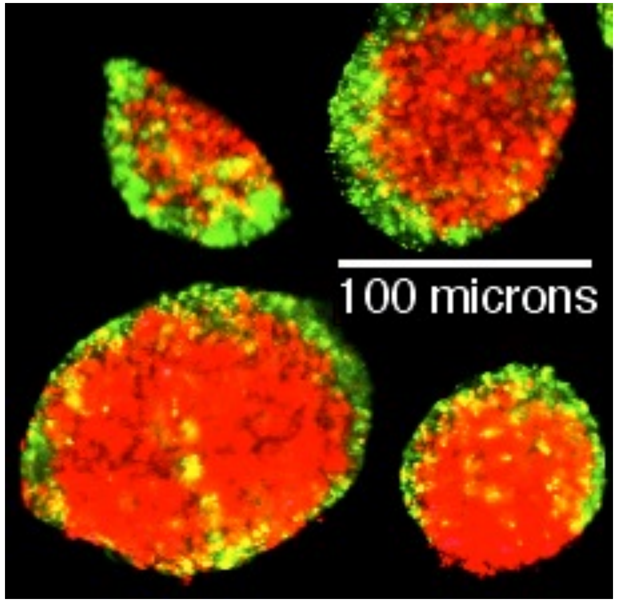

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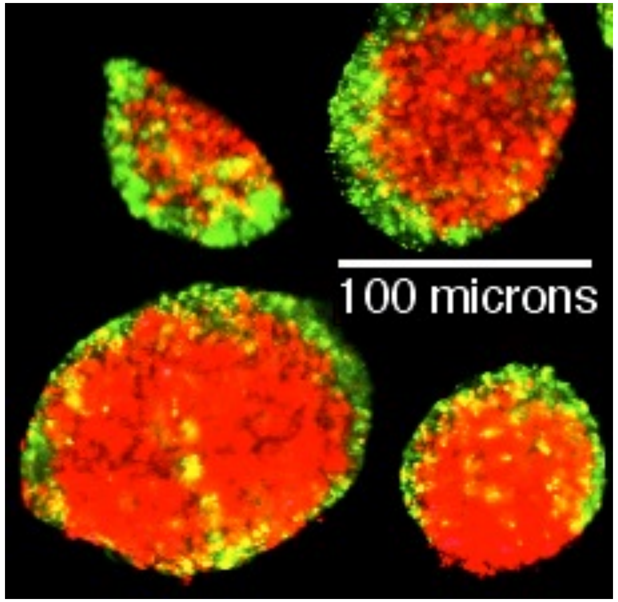

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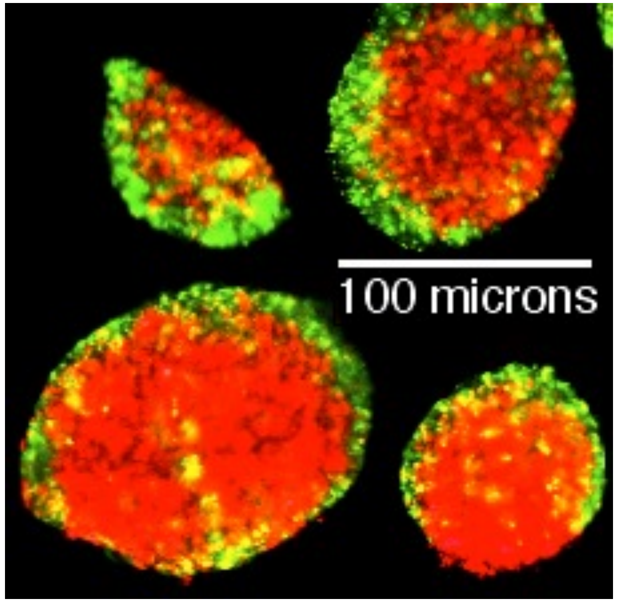

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Cells organize to minimize the total surface tension of the system

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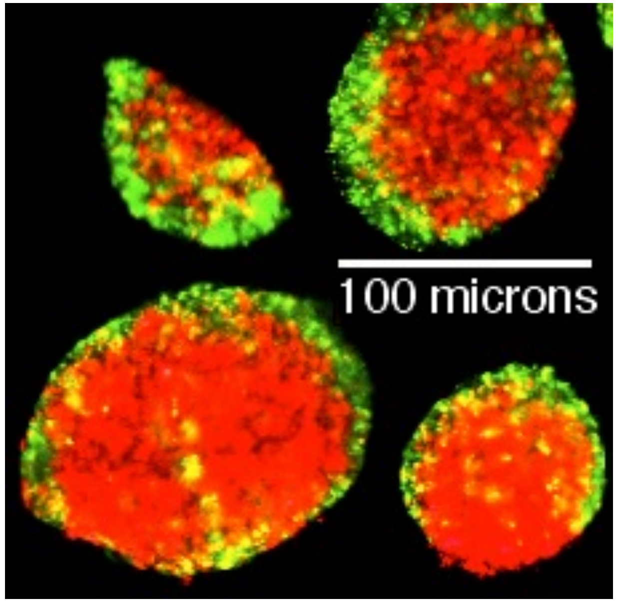

Morphogenesis. (2023, October 25).
In *Wikipedia*. https://en.wikipedia.org/wiki/Morphogenesis

Define: *m* for medium, *y* for yellow and *r* for red cells.

- To get engulfment of red cells by yellow cells, should $\gamma_{y,r} > 0$ or should $\gamma_{y,r} < 0$?
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- How about simple cell sorting and mosaic cell ordering?

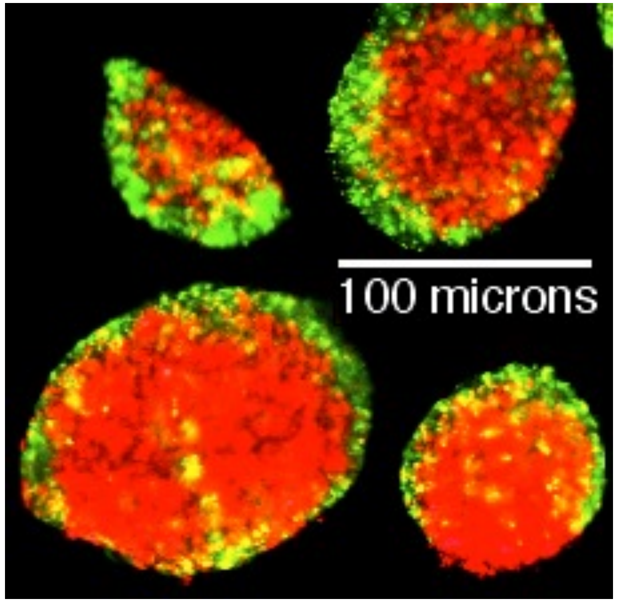
Original paper on CPM was on cell sorting: [1] Francois Graner and James A Glazier. Simulation of biological cell sorting using a two-dimensional extended Potts model. Physical review letters, 69(13):2013, 1992.
[2] Follow-up paper: Glazier, J. A., & Graner, F. (1993). Simulation of the differential adhesion driven rearrangement of biological cells. Physical Review E, 47(3), 2128.

$$H = \sum_{i,j \text{ neighbors}} J\left(\tau(\sigma_i), \tau(\sigma_j)\right)\left(1 - \delta(\sigma_i, \sigma_j)\right) + \lambda \sum_{\sigma_i} \left(v(\sigma_i) - V(\sigma_i)\right)^2,$$

Adhesion with neighbors

Resistance to volume changes

Solution! Cell sorting



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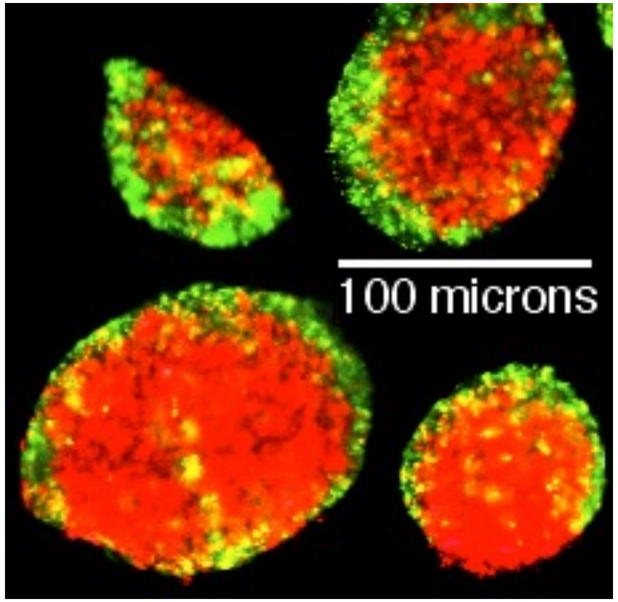

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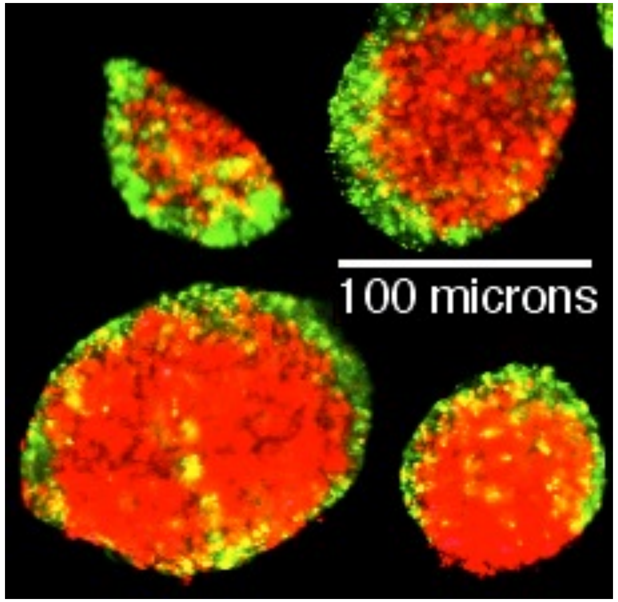

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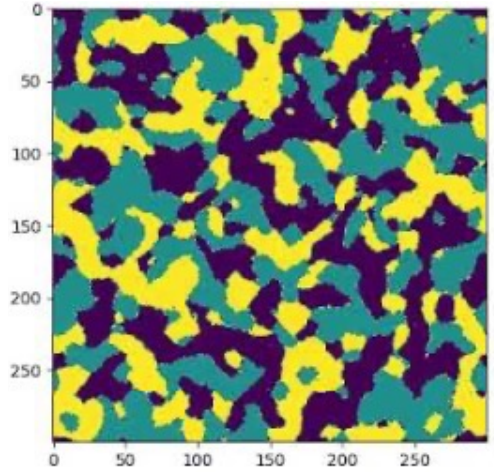
- **How about simple cell sorting (video)** and mosaic cell ordering? $\gamma_{y,r} > 0, \gamma_{y,m} = \gamma_{r,m} > 0$



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Morpheus

- Simulation exercise: https://www.uio.no/studier/emner/matnat/fys/FYS4715/h23/morphogenesis/
- Installation:
  - Instructions on gitlab: https://morpheus.gitlab.io/faq/installation/macos/
  - Install Homebrew (in Terminal): /bin/bash -c "$(curl -fsSL https://raw.githubusercontent.com/Homebrew/install/master/install.sh)”
  - brew tap morpheus-lab/Morpheus
  - brew install Morpheus
  - If you encounter problems, ask UIO GPT (much faster than IT Dept.)