Biological Physics

Modelling

(FYS4715)

1

Biological Modelling

- What is it?
  - Experiments on a computer
- Examples from lectures are very clean
- Purpose of lecture:
  - Demystify process
  - Highlight things to consider

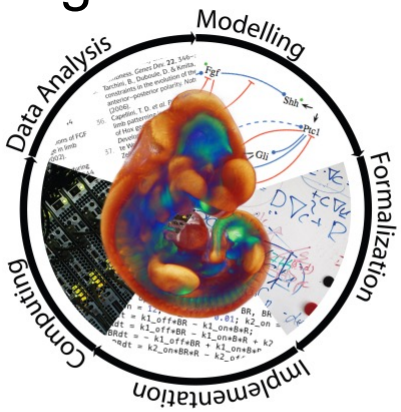


Figure 1: ***In silico* Models of Tissue Morphogenesis and Signaling.** Models are formulated based on available data. The formalized models then need to be implemented and solved. Model solutions are subsequently compared to available and newly generated data. Models are updated until a good match is achieved.

Iber

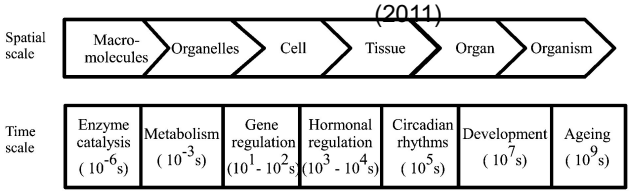
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Biological Modelling

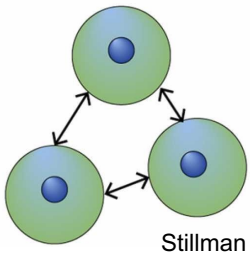
Always remember: biology is really really complicated.

- Multiple time and length scales interact non-linearly.
- Individual elements respond to their environment and act accordingly.
- Trade-offs are important.

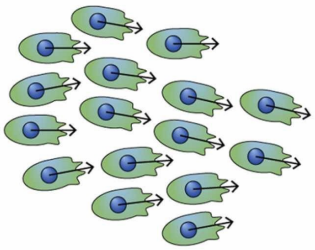
Dada & Mendes (2011)



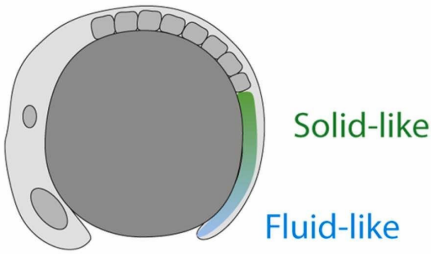
A
Cell-cell interactions



B
Collective cell migration



C
Morphogenesis



Stillman & Mayor (2020)

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Biological Modelling

- Why use modelling?
  - Reverse engineer mechanisms and test hypotheses
  - Total system knowledge
  - Total control of initial conditions
  - Speed of simulation
  - Sidestep ethical considerations
  - Interdisciplinarity looks good on grant applications

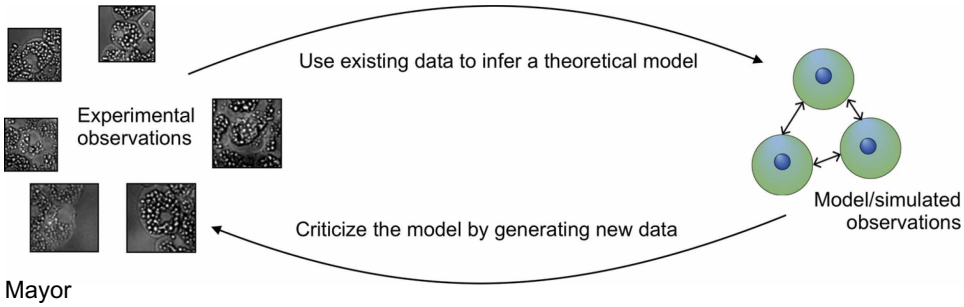
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Biological Modelling

Basic structure: (how do you do that bit on the right?)

Masters → PhD → post-doc → Professor, how much do you do?

- Have an idea
- Find/build a useful model
- Turn it into code
- Validate the code
- Results and extensions



Stillman & Mayor (2020)

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Case Study

Situation:

- You are a post-doc hired to do biological modelling as part of a larger project
- Integrated technologies for tracking organoid morphogenesis (ITOM)
- 4 work packages, tracking morphogenetic progresses
- WP4: Development of physical and statistical models that can feed into organoid development

Initial goals:

- Read the description and interact with group leaders
- Highlight key phrases you don't know and want to read up on
- Think of the implications for the model you will want to use
- You can't know everything

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WP4 Development of physical and statistical models that can feed into organoid development: Dag Kristian Dysthe and Hanne Røberg-Larsen and Luiza Angheluta (1PD at Physics Department)

Based on the data generated from WP1-3, we will develop and study minimal models of mechano-chemical interactions between cells and their self-organization into developing tissues with the aim to better understand collective cell behaviors involved during fundamental stages of organoid development that are observed by RSI analysis. Our theoretical approach is based on the representation of cells as self-propelled entities that transform chemical energy into motion, reproduction and interaction with other cells [5]. Cell division and interaction often lead to densely-packed cellular aggregates with the cohesive dynamics of a soft active matter which exhibit long-range orientational or polar order. Cell activity, however, tends to break this order through the spontaneous formation of orientational defects which induce flow and heterogeneous stress distribution in the cellular tissues. This feedback between activity and spontaneous symmetry-breaking turns out to play a key role during morphogenesis by controlling the onset and location of organ formation [6]. However, the details of that interplay are not fully understood or modelled. Within this theoretical framework, we will combine discrete models at the cell level with hydrodynamic models at the tissue level to better understand organoid morphogenesis as a self-organizing process through successive symmetry-breakings and emergent from cooperative cell-cell interactions. An advantage of the cell-based models, e.g. cellular Potts model, is the flexibility of tuning the cooperative interaction, which allows us to test different onsets of morphogenetic event in organoids and compare them with in-vitro experiments. In hydrodynamic models, we describe the large-scales dynamics of later-stage developing organoids that exhibit some orientational order of its constituent cells and their collective interactive patterns. The experimental data acquired in WPS 1-3 will be used to calibrate model parameters. Thus, the cell aggregate or hydrodynamic models tailored to the specific organoid models and reproducing some of morphogenetic patterns and cell motion observed experimentally will shed more lights on self-organization processes emergent from cell dynamics and cooperative interactions during morphogenesis. ***Deliverables: D12*** *Develop theoretical and computational minimal models of cell interactions and self-organization tailored to the experimental conditions used in Raman spectroscopy image analysis.* ***D13.*** *Modelling flow patterns in developing tissues during morphogenesis.* ***D14*** *Develop computational tracking tools to measuring the response to morphogen induced rhythmic perturbations.* ***D15*** *Data deposition at the HCA* Organoid database *(EU grant SC1-BHC-31-2019) and the tissue Image Data Resource (IDR).*

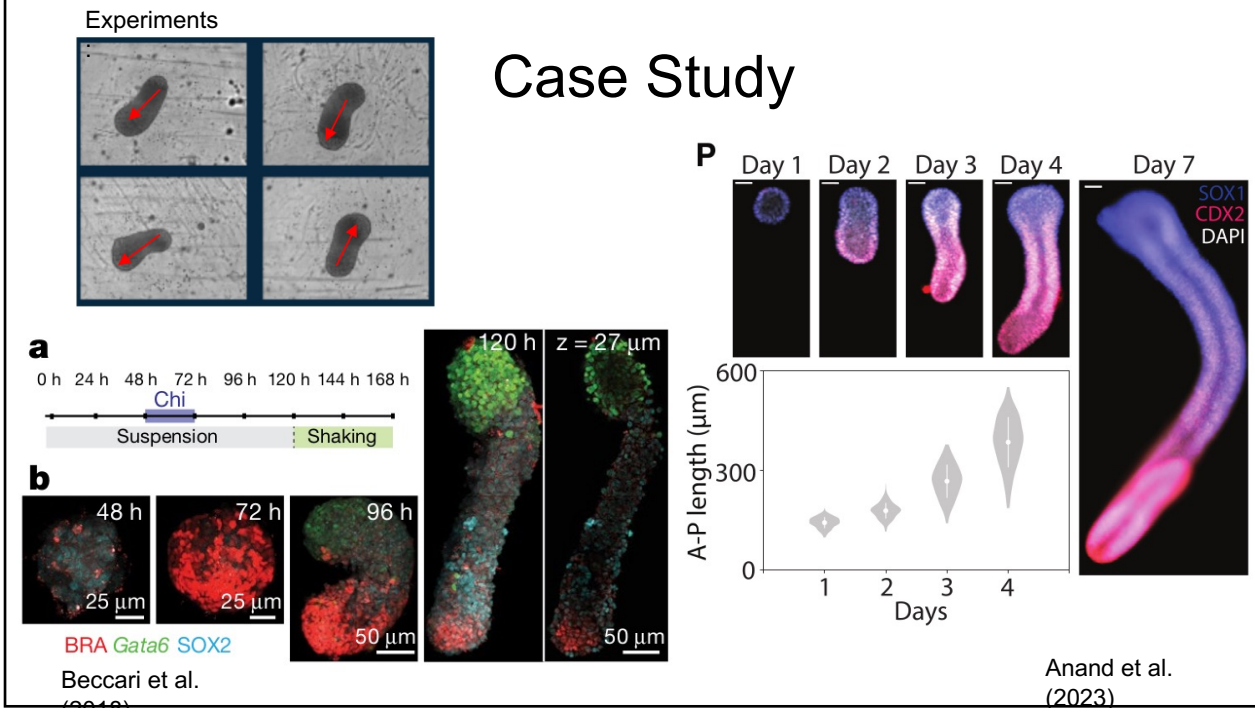
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Case Study

- “Based on data generated from WP1-3” need to calibrate our results
- “minimal models” the model needs to be simple
- “interactions between cells” need to model multiple cells
- “self-organisation into developing tissues” we do not want lots of external forcing
- “cells as self-propelled entities” we can ignore conservation of energy
- “cell division and interaction” we want to be able to model cell division
- “densely-packed cellular aggregates” the cells need to cohere into 3D tissues
- “long-range orientational or polar order” the tissues have structure, not just spheres
- “cell activity” we want to be able to add activity to any model we create
- “cell motion” we want to be able to quantify flows of cells

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Case Study



Beccari et al.

Anand et al. (2023)

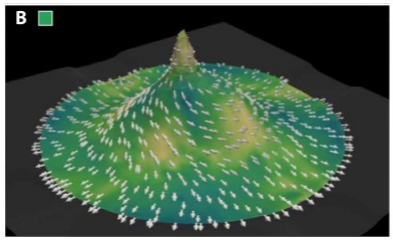
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Picking a Model

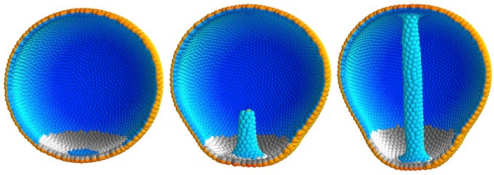
- You don't want to reinvent the wheel
- This is the most consequential decision you will make, no one ever changes model mid project:
  - Sunk costs
  - Difficult to tell people that you're not going to make progress for several months
  - Facility with the model increases with use
  - There are always trade-offs

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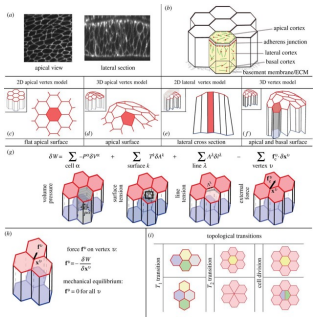
Picking a Model



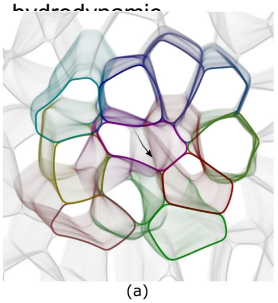
Hoffmann (2022),



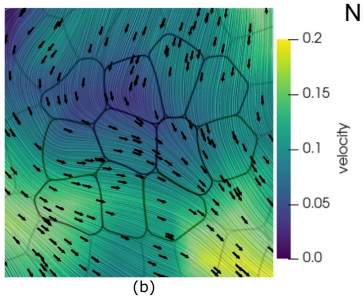
Nielsen (2020), discrete



Alt (2017), vertex



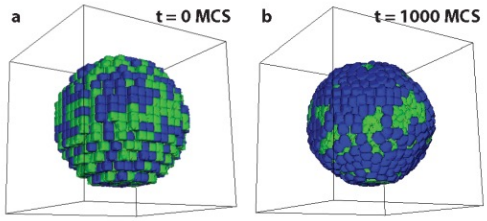
(a)



(b)

Jain (2023), phase field

Iber (2013), cellular Potts (CompuCell3D)



What sort of pros and cons can you think of in general?

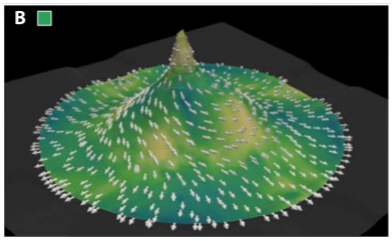
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Picking a Model

- Pros and cons: (there are always trade-offs, plus reference to original goals):
  - 2D vs 3D
  - level of abstraction
  - Number of parameters
  - Extendability of model
  - Computational cost (and parallelisation)
  - Continuum models vs Discrete
  - What you are familiar with (eg algorithms)
  - Visualisation
  - How well established the model is
  - Libraries/code accessibility
  - Other people's expertise
  - What new skills you need to learn

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Picking a Model



- Example of a rejected model (Hoffmann2022):
  - Look at these equations
  - Would need difficult differential geometry
  - New visualisation tools
  - 1 simulation = 35 CPUd (13 hrs real time)

Equations for surface:

$$0 = \eta\left(g_{ij}\nabla^i\nabla^j v^k + Kv^k\right) - \nabla^k P_\mathrm{h} + \nabla_j \sigma_\mathrm{a}^{jk} ,$$
$$v^k\nabla_k p^i = \left(g^{ij} - p^i p^j\right)\left(\lambda u_{jk}p^k - \omega_{jk}p^k + \Gamma h_j\right) .$$

$$F = \int_{\mathcal{M}} \mathrm{d}A \left[\gamma + \kappa_\mathrm{B}\left(H - H_0\right)^2 + \kappa_\mathrm{G}K + \frac{\kappa_\mathrm{F}}{2}\left(\nabla_i p_j\right)\left(\nabla^i p^j\right)\right] .$$

$$\Delta P = K^{ij}\left(-\Pi g_{ij} + 2\eta u_{ij} + \sigma_{\mathrm{a},ij}\right) + f_\mathrm{e}^n + f_\mathrm{p}^n$$

$$f_\mathrm{p}^n = 2\kappa_\mathrm{F}(2Hg^{ij} - K^{ij})\nabla_i\nabla_j\chi + 2\kappa_\mathrm{F}(K^{ij} - Hg^{ij})\nabla_i\chi\nabla_j\chi$$

$$f_\mathrm{e}^n = 2\gamma H - \kappa_B\left\{\Delta H - \left(H - H_0\right)\left[2H(H - H_0) - 4H^2 + 2K\right]\right\}$$

Equations for bulk:

$$f_\phi = a\frac{\phi^2(\phi - \phi_0)^2}{\phi_\mathrm{n}^2} + \frac{k_\phi}{2}(\nabla\phi)^2 ,$$
$$\left(\partial_t + \boldsymbol{v}\cdot\nabla\right)\phi = \nabla\cdot\left(\mu\nabla\frac{\delta\mathcal{F}}{\delta\phi}\right) ,$$
$$\left(\partial_t + \boldsymbol{v}\cdot\nabla\right)\boldsymbol{\Psi}_n = \boldsymbol{\Omega}_n + \Gamma\boldsymbol{h}_n ,$$
$$\rho(\partial_t + \boldsymbol{v}\cdot\nabla)\boldsymbol{v} = \nabla\cdot\left(\boldsymbol{\sigma}_\mathrm{h} + \boldsymbol{\sigma}_\phi + \boldsymbol{\sigma}_\mathrm{p} + \boldsymbol{\sigma}_\mathrm{a}\right) .$$

$$f_\mathrm{p} = A_0\left(\frac{\psi}{2}\left|\boldsymbol{\Psi}_1\right|^2 + \frac{1}{4}\left|\boldsymbol{\Psi}_1\right|^4\right) + \frac{\kappa_\mathrm{F}}{2}\left|\nabla\boldsymbol{\Psi}_1\right|^2 ,$$
$$f_\mathrm{c} = \frac{\beta}{2}\left(\boldsymbol{\Psi}_1\cdot\nabla\phi\right)^2 .$$

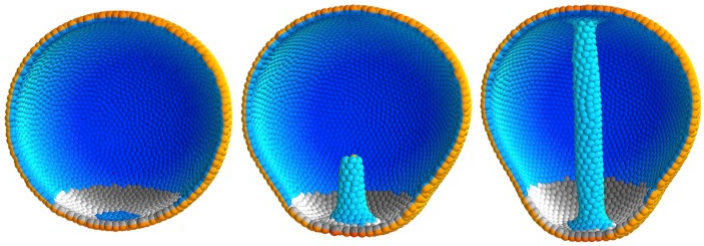
$$\boldsymbol{\sigma}_\mathrm{e} = \frac{1}{2}\left(\boldsymbol{\Psi}_1\boldsymbol{h}_1 - \boldsymbol{h}_1\boldsymbol{\Psi}_1\right) - \frac{\lambda}{2}\left(\boldsymbol{\Psi}_1\boldsymbol{h}_1 + \boldsymbol{h}_1\boldsymbol{\Psi}_1\right) - \kappa_\mathrm{F}\nabla\boldsymbol{\Psi}_1\cdot\left(\nabla\boldsymbol{\Psi}_1\right)^\mathrm{T} ,$$
$$\boldsymbol{\sigma}_\mathrm{c} = -\beta\boldsymbol{\Psi}_1\nabla\phi ,$$
$$\boldsymbol{\sigma}_\mathrm{a} = \alpha\left(\boldsymbol{\Psi}_1\boldsymbol{\Psi}_1 - \frac{1}{3}\left|\boldsymbol{\Psi}_1\right|^2\mathbb{1}\right) ,$$

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Turning the model from paper to code

Advantages:

- allows 3D
- easy visualisation
- easy to gain intuition
- relatively “new”



Nielsen (2020)

Particle/Discrete models are relatively simple:

- How do particles interact
- Which particles interact

To do:

- See if their code can be modified
- Try to turn their paper into code (this is sometimes easier said than done)

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Turning the model from paper to code

Their version of the code:

Declaration of Interests

The authors declare no competing interests.

Data and Code Availability

Download all supplementary files included with this article

The source code for the simulations is available on GitHub (Nielsen, 2019).

```
# Calculate potential
V, self.true_neighbour_max = potential(x, p, q, idx, d, lam, alpha, z_mask, dx, m)

# Backpropagation
V.backward()

# Time-step
with torch.no_grad():
    x += -x.grad * dt + eta * float_tensor(*x.shape).normal_() * sqrt_dt
    p += -p.grad * dt + eta * float_tensor(*x.shape).normal_() * sqrt_dt
    # q is kept fixed
    #q += -q.grad * dt + eta * float_tensor(*x.shape).normal_() * sqrt_dt
```

The entire readme:

```
Code for simulation of Gastrulation. Output will be placed in
./mats_# where # is an identifier. It can be visualized by running
singleplotn.py with # as the first argument.
```

```
pti = pti/torch.sqrt(torch.sum(pti ** 2, dim=2))[:, :, None]
ptj = ptj/torch.sqrt(torch.sum(ptj ** 2, dim=2))[:, :, None]


#S1 = torch.sum(torch.cross(pj, dx, dim=2) * torch.cross(pi, dx, dim=2), dim=2)
S1 = torch.sum(torch.cross(ptj, dx, dim=2) * torch.cross(pti, dx, dim=2), dim=2)
S2 = torch.sum(torch.cross(pi, qi, dim=2) * torch.cross(pj, qj, dim=2), dim=2)
S3 = torch.sum(torch.cross(qi, dx, dim=2) * torch.cross(qj, dx, dim=2), dim=2)

#S = z_mask.float() * (lam[0] * S1 + lam[1] * S2 + lam[2] * S3)
S = lam[:,:,0] * S1 + lam[:,:,1] * S2 + lam[:,:,2] * S3
# Add heaviside function
#S = (S>0).float()*S;

# Potential
Vij = z_mask.float() * (torch.exp(-d) - S * torch.exp(-d/5))
V = torch.sum(Vij)

return V, int(m)
```

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Turning the model from paper to code

How do particles interact?

$$\frac{d\bar{r}_i}{dt} = -\frac{dV_i}{d\bar{r}_i} + \eta,$$

$$\frac{d\bar{p}_i}{dt} = -\frac{dV_i}{d\bar{p}_i} + \eta,$$

$$\frac{d\bar{q}_i}{dt} = -\frac{dV_i}{d\bar{q}_i} + \eta,$$

$$V_i = \sum_j V_{ij}.$$

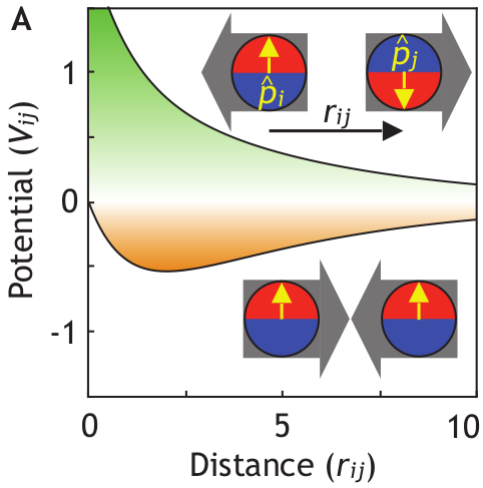
$$S_1 = (\hat{p}_i \times \hat{r}_{ij}) \cdot (\hat{p}_j \times \hat{r}_{ij}).$$

$$S_2 = (\hat{p}_i \times \hat{q}_i) \cdot (\hat{p}_j \times \hat{q}_j),$$

$$S_3 = (\hat{q}_i \times \hat{r}_{ij}) \cdot (\hat{q}_j \times \hat{r}_{ij}).$$

$$S = \lambda_1 S_1 + \lambda_2 S_2 + \lambda_3 S_3$$

$$V_{ij} = e^{-r_{ij}} - S\, e^{-r_{ij}/\beta},$$



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Turning the model from paper to code

Explicit interaction rules written down:

$$\frac{dV_{ij}}{d\bar{r}_i} = e^{-r_{ij}/\beta}\left\{ \gamma\, \hat{r}_{ij} - \frac{\lambda_1}{r_{ij}}\left[(\hat{r}_{ij}\cdot\hat{p}_j)\hat{p}_i + (\hat{r}_{ij}\cdot\hat{p}_i)\hat{p}_j\right] - \frac{\lambda_3}{r_{ij}}\left[(\hat{r}_{ij}\cdot\hat{q}_j)\hat{q}_i + (\hat{r}_{ij}\cdot\hat{q}_i)\hat{q}_j\right]\right\},$$

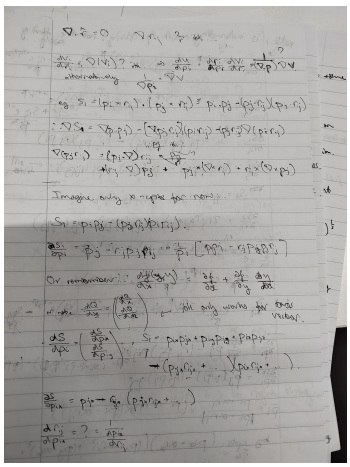
$$\frac{dV_{ij}}{d\bar{p}_i} = e^{-r_{ij}/\beta}\left\{ \lambda_1\left[S_1\hat{p}_i - \hat{p}_j + (\hat{r}_{ij}\cdot\hat{p}_j)\hat{r}_{ij}\right] + \lambda_2\left[S_2\hat{p}_i - (\hat{q}_i\cdot\hat{q}_j)\hat{p}_j + (\hat{q}_i\cdot\hat{p}_j)\hat{q}_j\right]\right\},$$

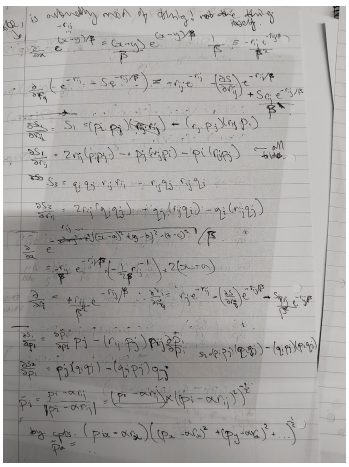
$$\frac{dV_{ij}}{d\bar{q}_i} = e^{-r_{ij}/\beta}\left\{ \lambda_2\left[S_2\hat{q}_i - (\hat{p}_i\cdot\hat{p}_j)\hat{q}_j + (\hat{p}_i\cdot\hat{q}_j)\hat{p}_j\right] + \lambda_3\left[S_3\hat{q}_i - \hat{q}_j + (\hat{r}_{ij}\cdot\hat{q}_j)\hat{r}_{ij}\right]\right\}.$$

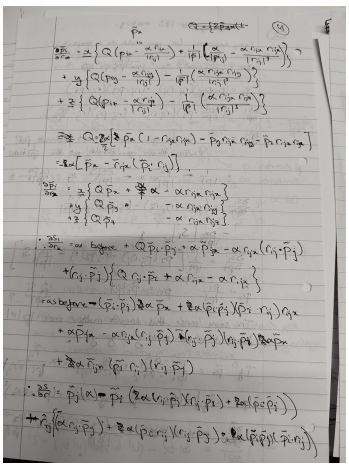
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Turning the model from paper to code

Attempts to re-derive these equations:



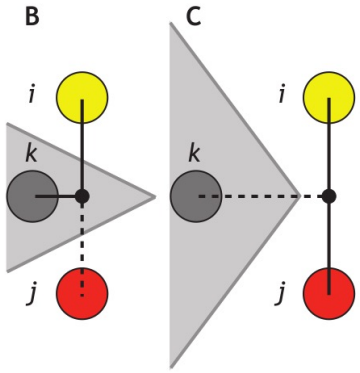




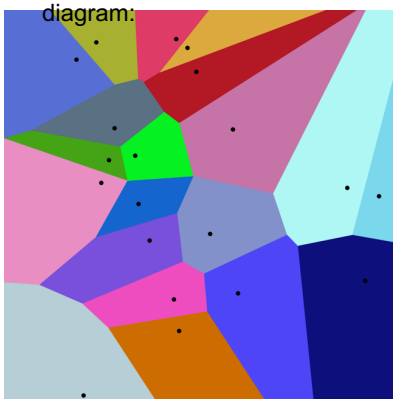
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Turning the model from paper to code

Which particles interact:



Voronoi diagram:

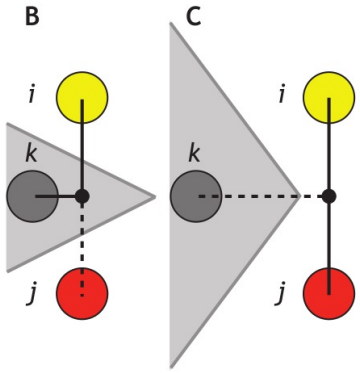


Two cells interact only if no other cells block the line of sight between them. (**B**) Cell *i* and *j* do not interact if *ij*'s midpoint (black dot) is inside of the Voronoi diagram for cell *k* (shaded in grey). (**C**) Cell *i* and *j* interact because cell *k* is further away than the distance *ij*/2 and *ij*'s midpoint therefore lie outside of cell *k*'s Voronoi diagram.

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Turning the model from paper to code

Which particles interact:



$$r_{ij}^2 < r_{ik}^2 + r_{jk}^2 \text{ for all other } k$$

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Validation

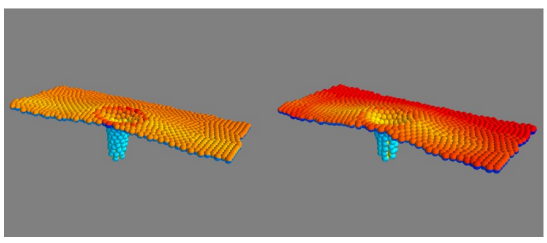
- Sanity checks (calibration may exist in PhD theses)
- Recreation of “interesting” results
- Validation is not what you wanted to do, but it needs to be done

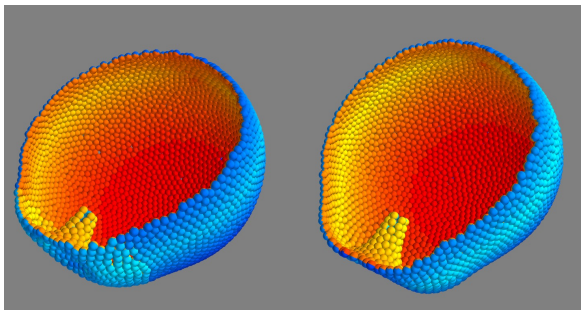
Key rule: If a result is interesting or inexplicable, it is most likely to be a bug in your code

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Validation

- Recreation of old results: (old vs new)

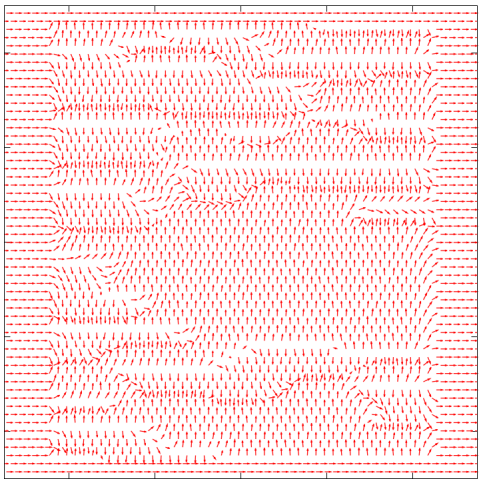


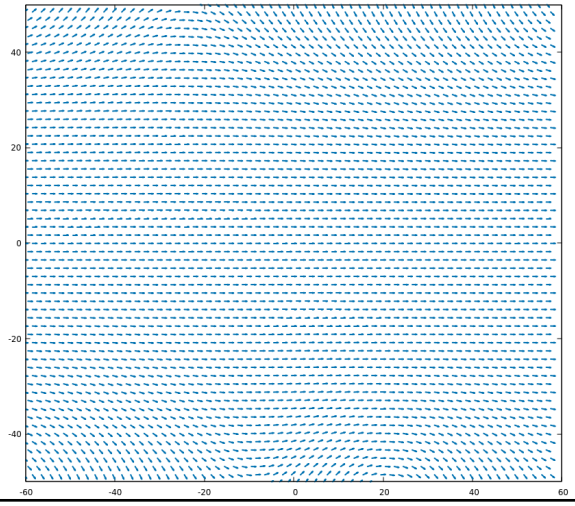


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Validation

- Sanity checks: (incorrect vs. correct)





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Results and Extensions

- Now we can actually go back to the original questions
- May need to extend model, with each extension, sanity checks need to be made
- Benefit of using less well used model: can now explore lots of situation that others haven't, also can examine model on its own outside of original motivation
- Here are some things that we have found in the model

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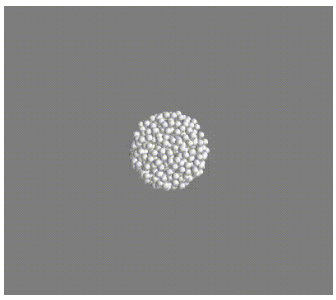
Results and Extensions

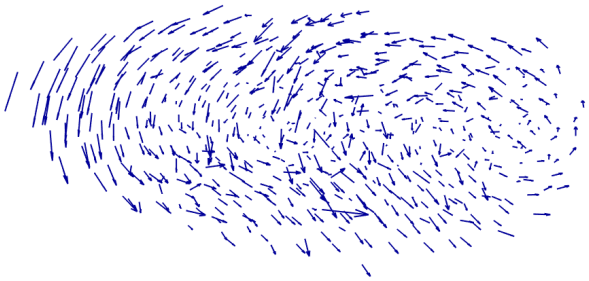
- Add isotropic force, can get aggregates
- Can run fast (few minutes), and track everything

$$V_{ij} = (1 + \lambda_0)e^{-r_{ij}} - (\lambda_0 + \lambda_1 S_1 + \lambda_2 S_2 + \lambda_3 S_3)e^{-r_{ij}/\beta}$$

$$S_1 = (p_i \times r_{ij}) \cdot (p_j \times r_{ij}) \,,\; S_2 = (p_i \times q_i) \cdot (p_j \times q_j) \,,\; S_3 = (q_i \times r_{ij}) \cdot (q_j \times r_{ij})$$

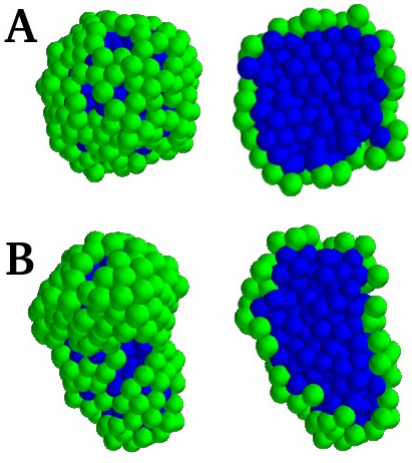
$$\frac{\partial r_i}{\partial t} = -\frac{\partial V_i}{\partial r_i} + \eta \,,\; \frac{\partial p_i}{\partial t} = -\frac{\partial V_i}{\partial p_i} + \eta \,,\; \frac{\partial q_i}{\partial t} = -\frac{\partial V_i}{\partial q_i} + \eta$$



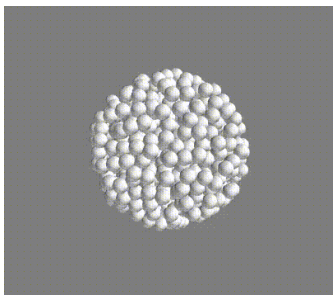


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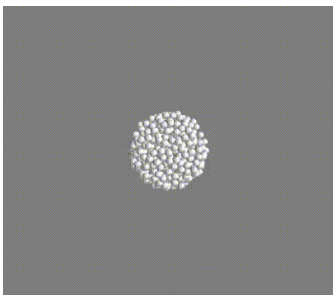
Elongation and neighbour requirement:



With neighbour req:



Without neighbour req:

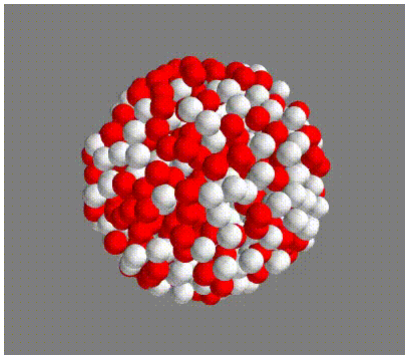


Only blue cells contribute to elongation

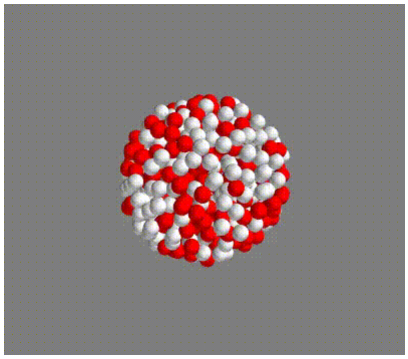
26

26

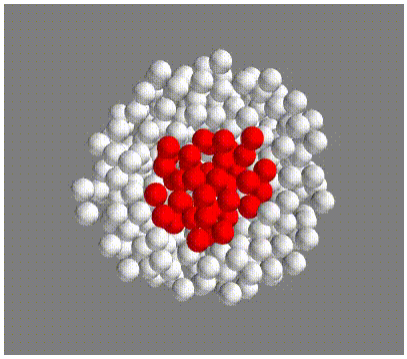
Polarity can help cell sorting



Pure differential adhesion



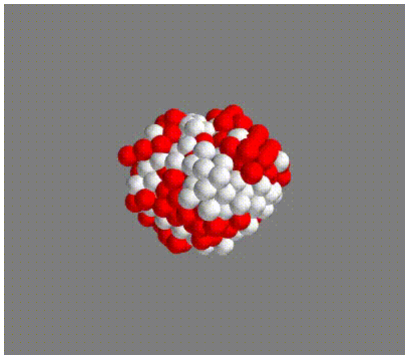
With polarities

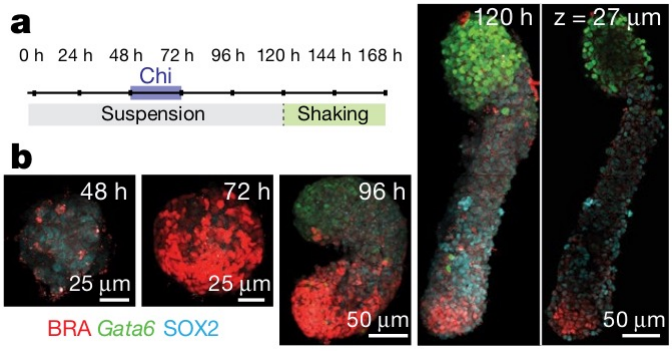


Blastocyst like object

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Two phase separation with subsequent elongation

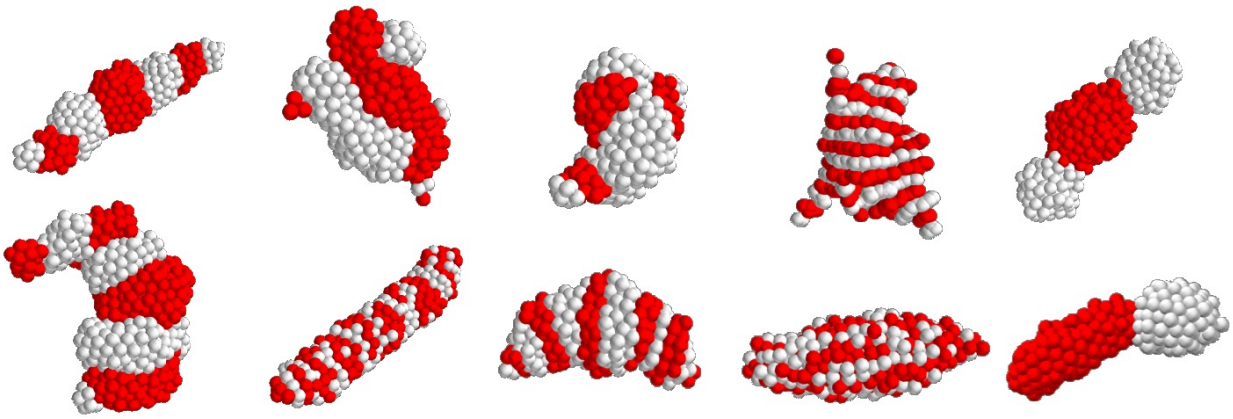




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Sponteneous elongation for two cell species



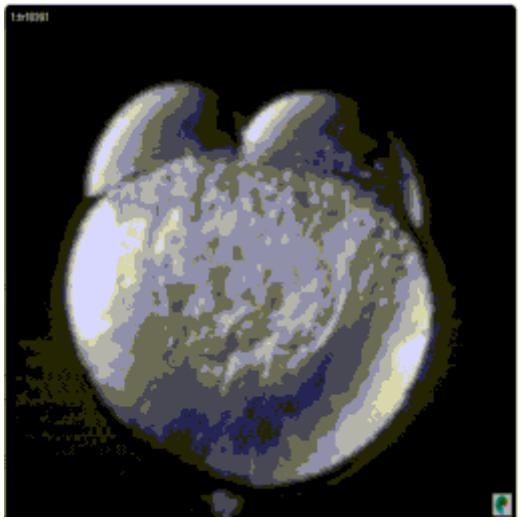
- Tissue elongation is induced by adhesion forces between the same type of polarised cells
- Tissue elongation saturates when cells have a minimum number of contact neighbours.
- Depending on rules and parameters, many outcomes are possible.

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Response (1 year later)

Also, try this instead:



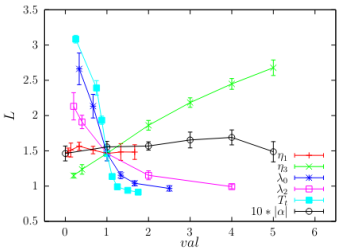
30

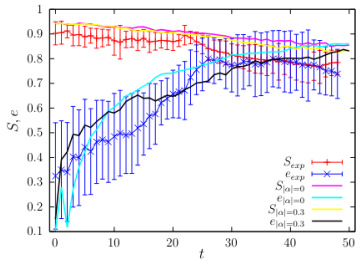
Response (1 year later)

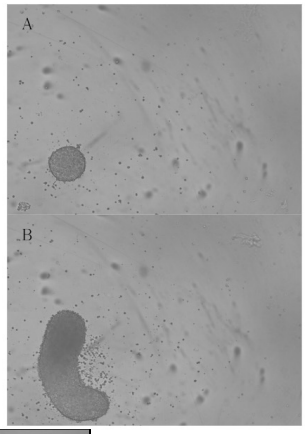
reproduction and interaction with other cells [5]. Cell division and interaction often lead to densely-packed cellular aggregates with the cohesive dynamics of a soft active matter which exhibit long-range orientational or polar order. Cell activity, however, tends to break this order through the spontaneous formation of orientational defects which induce flow and heterogeneous stress distribution in the cellular tissues. This feedback between activity and spontaneous symmetry-breaking turns out to play a key role during morphogenesis by controlling the onset and location of organ formation [6]. However, the details of that interplay are not fully understood or modelled. Within this theoretical framework, we will combine discrete models at the cell level with hydrodynamic models at the tissue level to better understand organoid morphogenesis as a self-organizing process through successive symmetry-breakings and emergent from cooperative cell-cell interactions. An advantage of the cell-based models, e.g. cellular Potts model, is the flexibility of tuning the cooperative interaction, which allows us to test different onsets of morphogenetic event in organoids and compare them with in-vitro experiments. In hydrodynamic models, we describe the large-scales dynamics of later-stage developing organoids that exhibit some orientational order of its constituent cells and their collective interactive patterns. The experimental data acquired in WPS 1-3 will be used to calibrate model parameters. Thus, the cell aggregate or hydrodynamic models tailored to the specific organoid models and reproducing some of morphogenetic patterns and cell motion observed experimentally will shed more lights on self-organization processes emergent from cell dynamics and cooperative interactions during morphogenesis. ***Deliverables: D12*** *Develop theoretical and computational minimal models of cell interactions and self-organization tailored to the experimental conditions used in Raman spectroscopy image analysis.* ***D13.*** *Modelling flow patterns in developing tissues during morphogenesis.* ***D14*** *Develop computational tracking tools to measuring the response to morphogen induced rhythmic perturbations.* ***D15*** *Data deposition at the HCA* Organoid database *(EU grant SC1-BHC-31-2019) and the tissue Image Data Resource (IDR).*

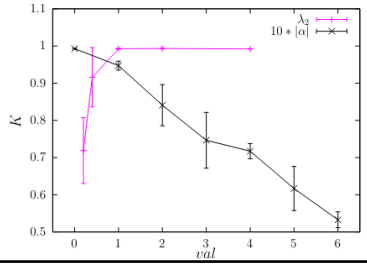
31

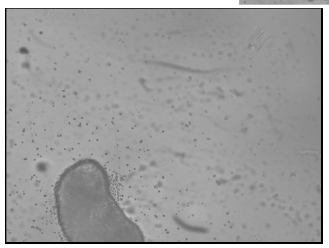
Result (1 year later)











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Result (1 year later)

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Role of tissue fluidization and topological defects in epithelial tubulogenesis

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ABSTRACT

Cellular rearrangements, as primary sources of tissue fluidization, facilitate topological transitions during tissue morphogenesis. We study the role of intrinsic cell properties such as cell polarity and cell-cell adhesion in shaping epithelial tissues using a minimal model of interacting polarized cells. The presence of a vortex in the cell polarization poses the topological constraint that induces an inwards migration with the formation of a conical shape. Local rearrangements at the tip of the cone lead to the onset of tube formation. Switching between collective migration and structural rearrangements is key for balancing the contrasting tendencies, such as the tissue rigidity needed to preserve shape and the tissue fluidity allowing for topological transitions during tissue morphogenesis.

