Understanding collective phenomena in multicellular systems through agent-based models

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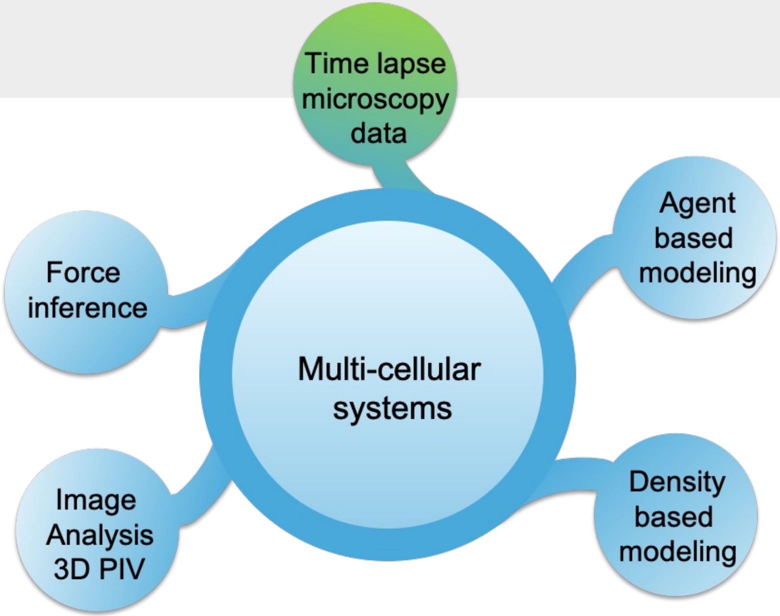
Research Overview



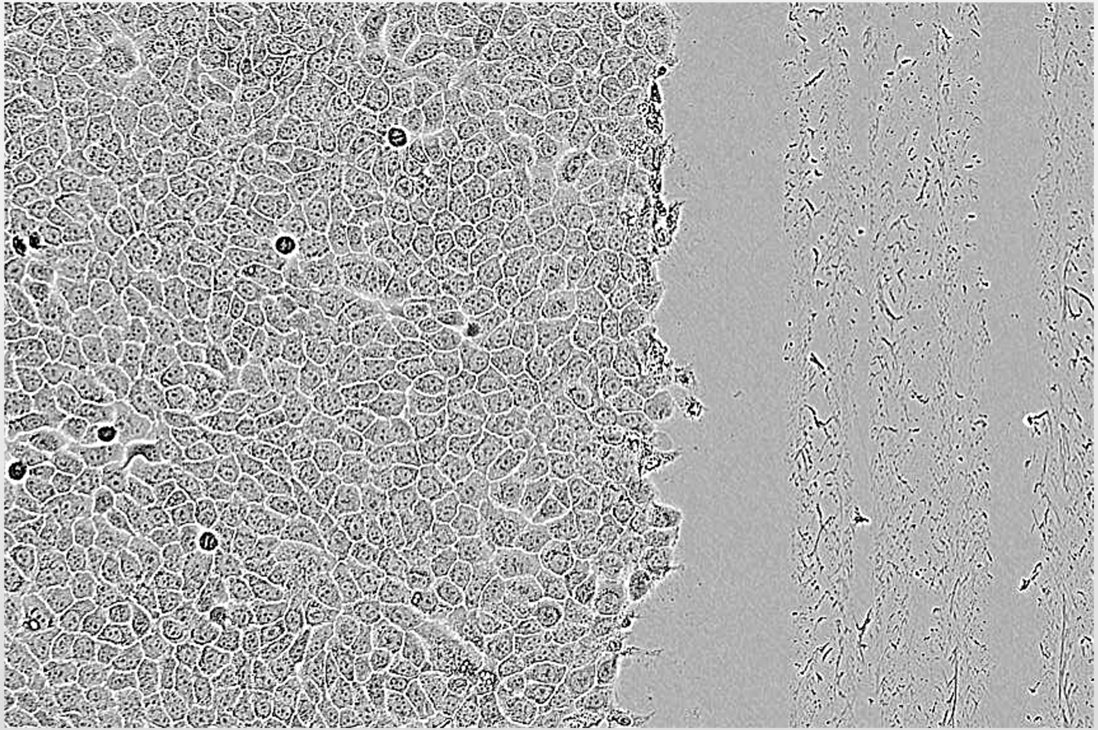
Multi-cellular systems exhibit a range of behaviors that can be studied using agent-based approaches;

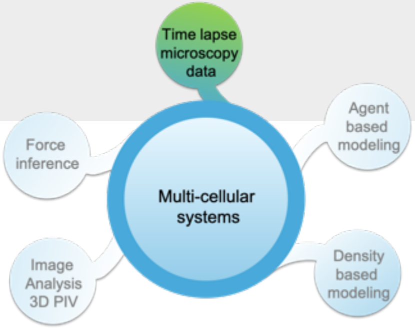
- Collective phenomena
- Self-organization & pattern formation
- Structure – function relationship
- mechano-chemical regulation
- Active vs. passive mechanisms in biological systems

Goal:

The identification of ***simple principles*** of complex behavior:
How does ***local information*** generate ***global structure***?

Applications in Life Sciences





2D / 3D time-lapse microscopy data

Wound healing
(with AK Windbergs, FB 14)

Skin patterning
(With D. Headon, Roslin Institute, UK)

Organoid dynamics
(with AK Stelzer, FB 15)

Development
(with AK Stelzer, FB 15, J. Rainger
& D. Headon, Roslin Institute, UK)

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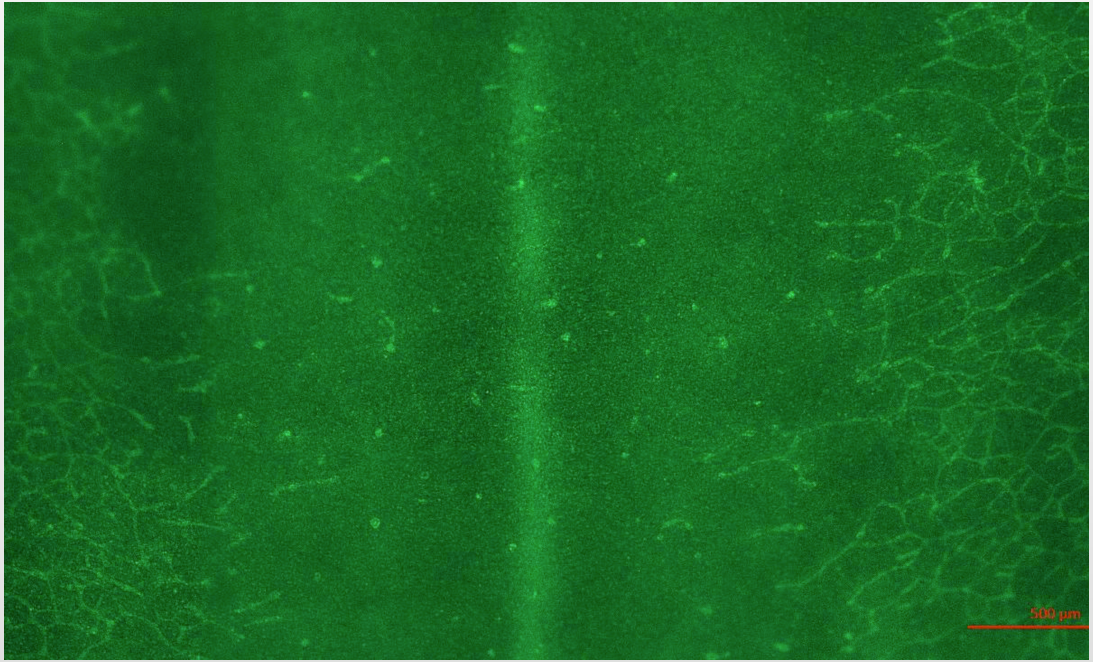

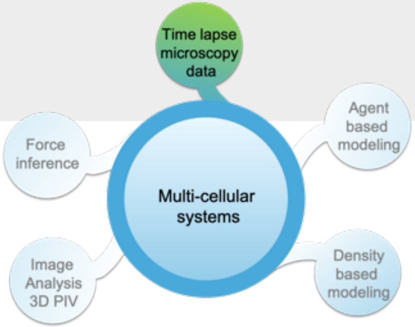

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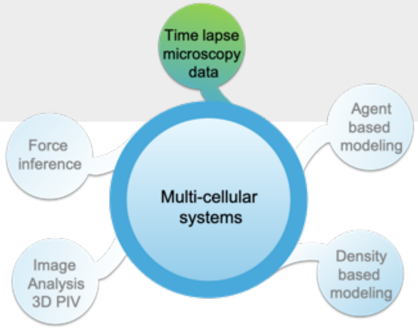

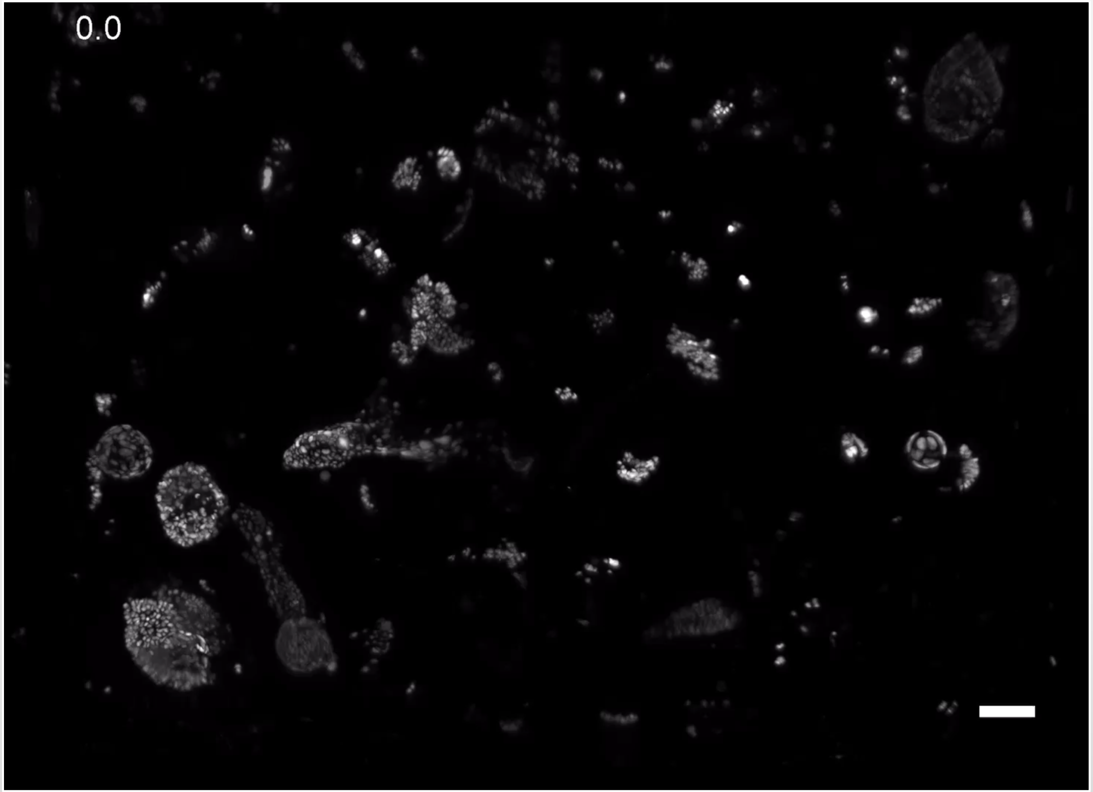

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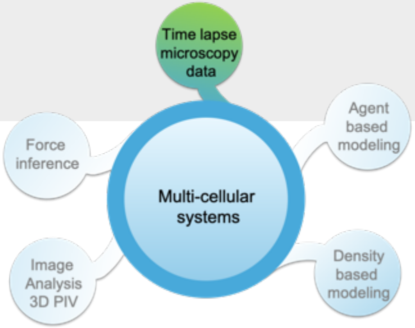

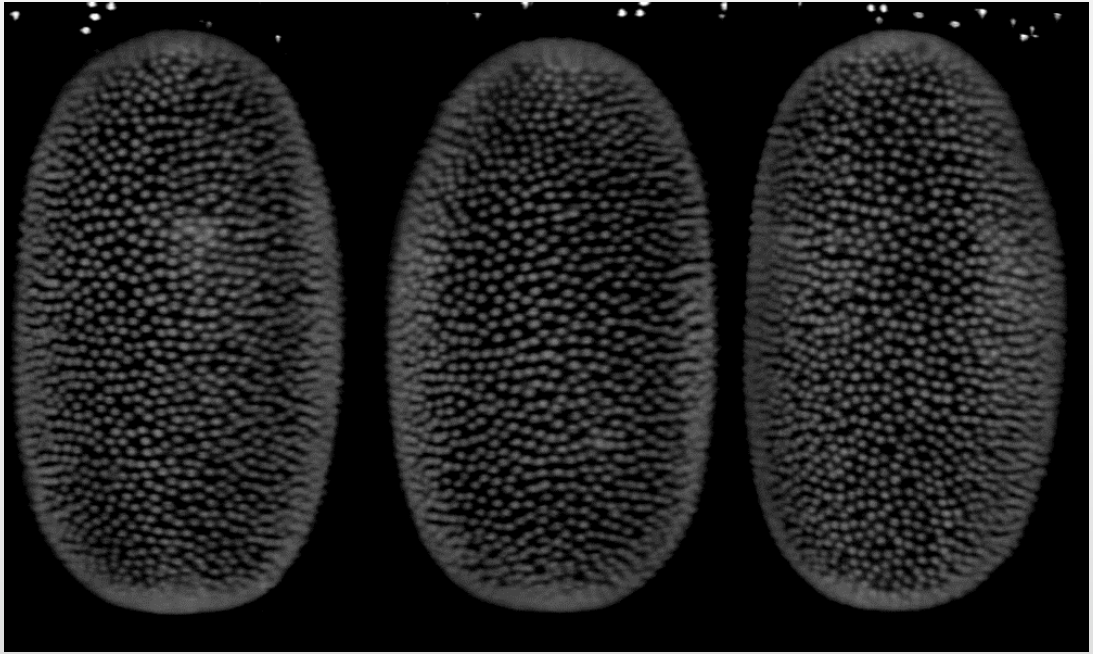

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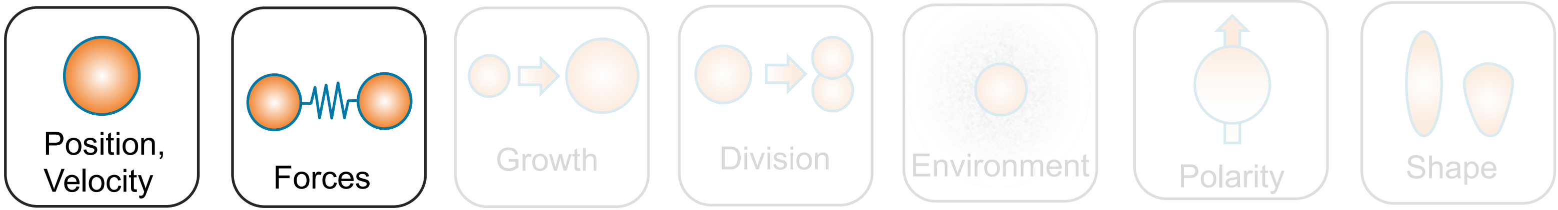
Agent-based modeling toolkit

Agent-based Modeling Toolkit



Centroid position adhesion/repulsion

$$\frac{\partial \boldsymbol{x}_i}{\partial t} = \sum_{j \in N} \boldsymbol{F}_{i,j} + \boldsymbol{v} + \boldsymbol{\xi}(t)$$

← random motion

Active migration

$$\frac{\partial \boldsymbol{v}}{\partial t} = \frac{1}{\tau}\left(\sum_{j \in N} \boldsymbol{F}_{i,j} - \boldsymbol{v}\right)$$

mechanotransduction, persistence, friction

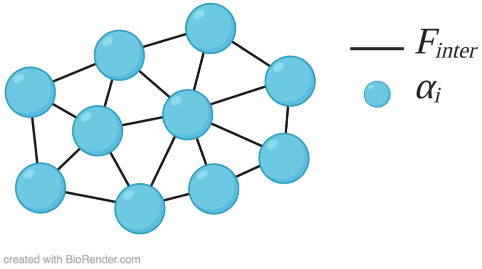
Forces

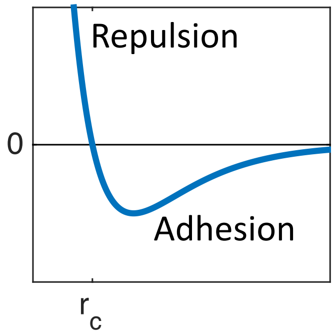
$$\boldsymbol{F} = F_0 \cdot F(||\boldsymbol{x}_i - \boldsymbol{x}_j||)\frac{\boldsymbol{x}_i - \boldsymbol{x}_j}{||\boldsymbol{x}_i - \boldsymbol{x}_j||}$$

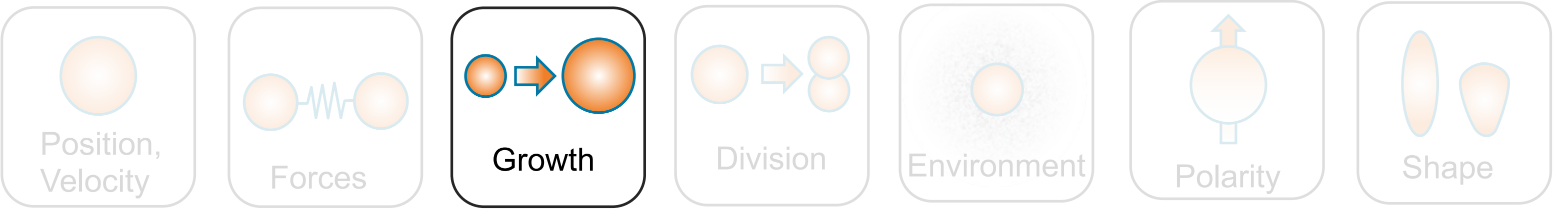
Force potential

$$F(r) = \begin{cases} 2 \cdot e^{-2a(r-r_c)} - e^{-a(r-r_c)}, & r < \sigma r_c \\ 0, & r \geq \sigma r_c \end{cases}$$

Cell neighborhood via Gabriel net (distance based) or Delaunay triangulation

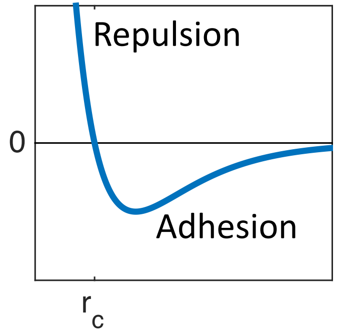


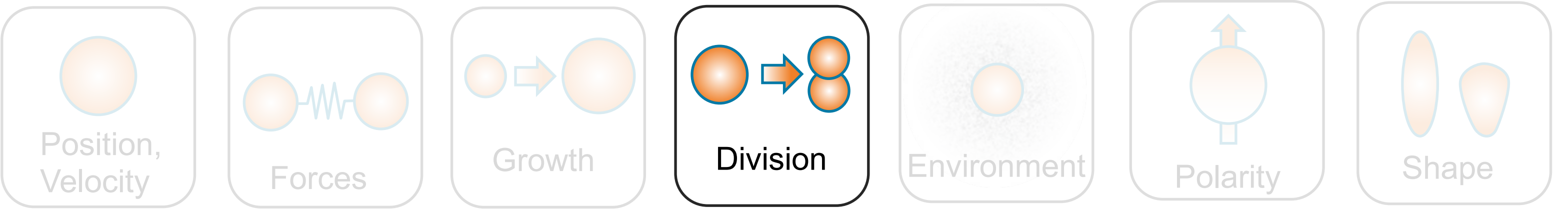




Pressure-dependent cell growth

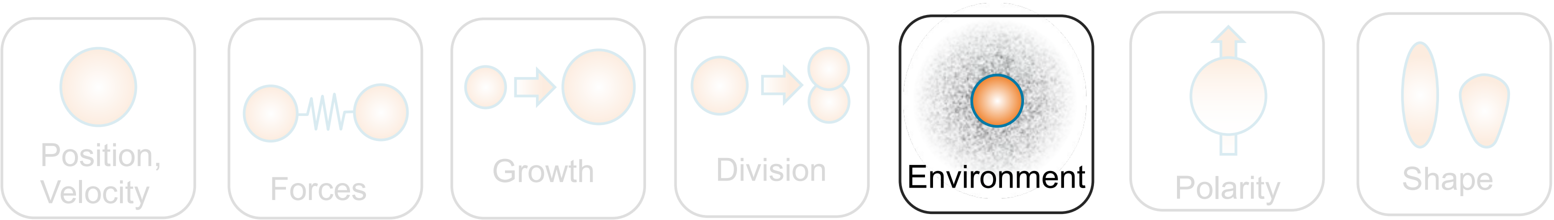
$$\frac{dr_i}{dt} = k(\hat{F}_i, |v_i|) \cdot (r_{max} - r_i)$$





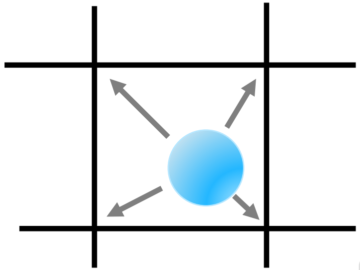
Division (rule-based):

- a second cell centroid is placed in close proximity to the mother centroid
- optional: both cell radii are reduced for volume preservation: $r_d = \sqrt[3]{1/2} \cdot r_m$
- local mechanics automatically adjusts position of new cells



Chemical environment:

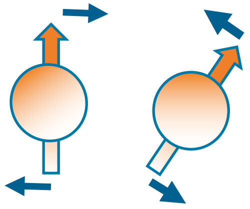
- Spatio-temporal dynamics of compounds given by systems of partial differential equations
- Sensing and production of chemicals: coupling off-lattice positions to numerical grid
- Active motion term extended by chemotaxis

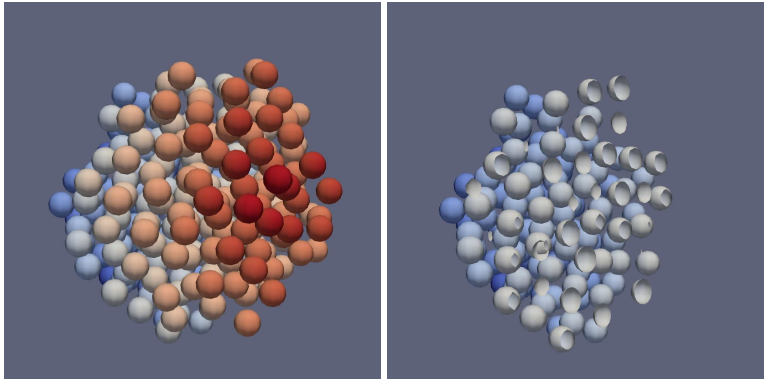


This results in hybrid discrete-continuous models!

Agent-based Modeling Toolkit

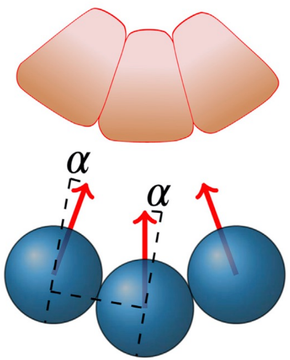
Spin-dependent force potential

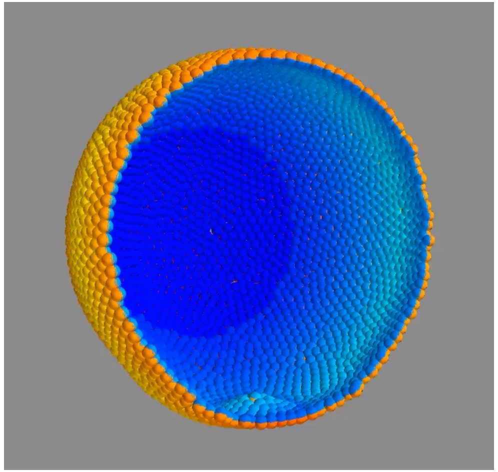




Nissen et al., eLife, 2018

Agent-Based Modeling Toolkit





Nielsen et al., iScience, 2020

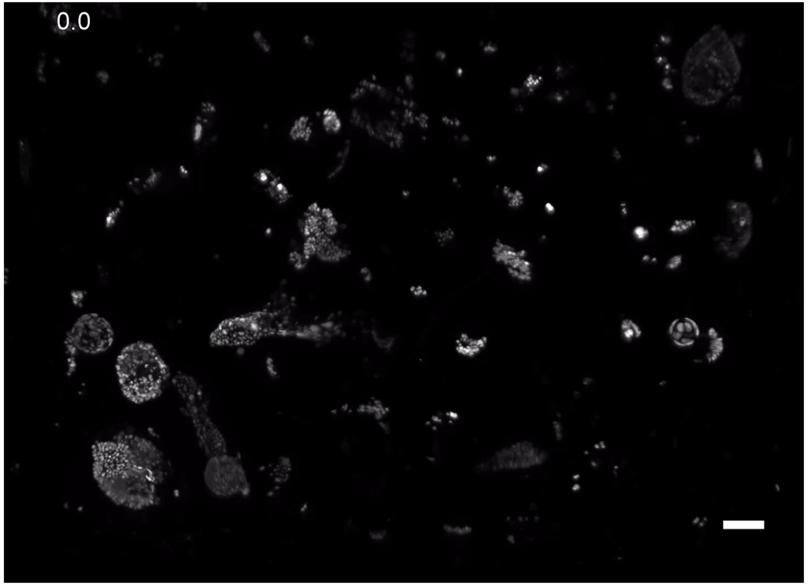
Quantiative Data is Needed for Model Design

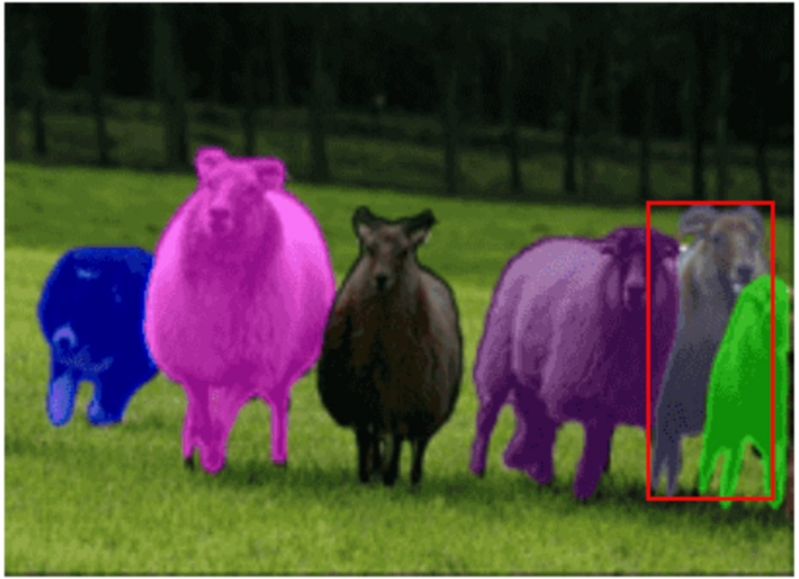
How do we 'inform' the models?

To develop the structure of the model (which processes to include) we need hypotheses/relations (qualitative data)

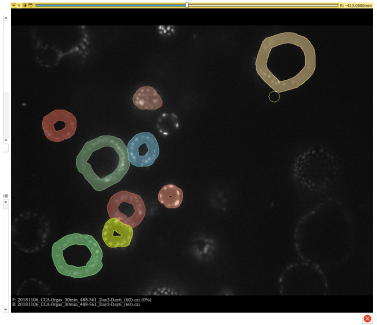
To parametrize the models we need quantitative data

Instance segmentation (mask_rcnn) [M. Pereyra]



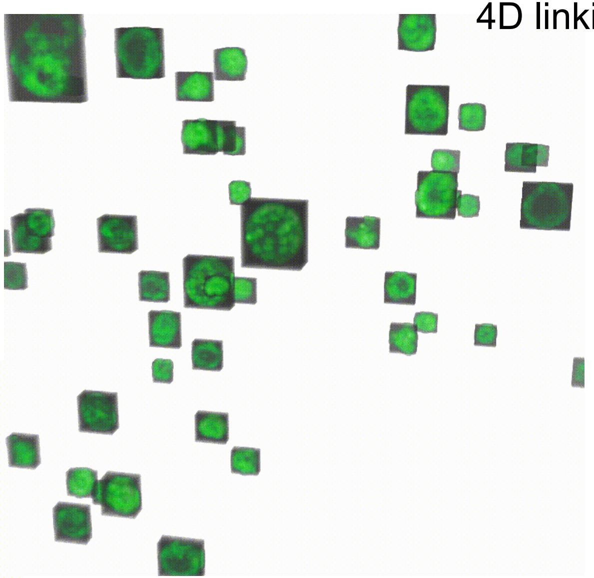


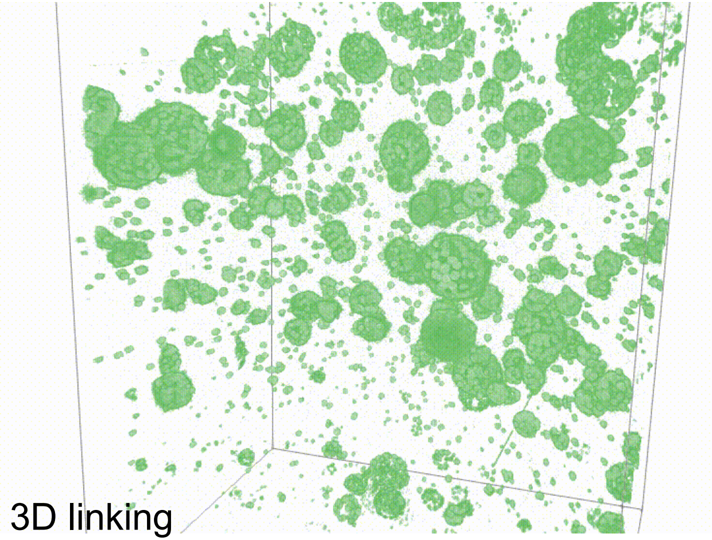
Object identification



2D Annotation
training & prediction

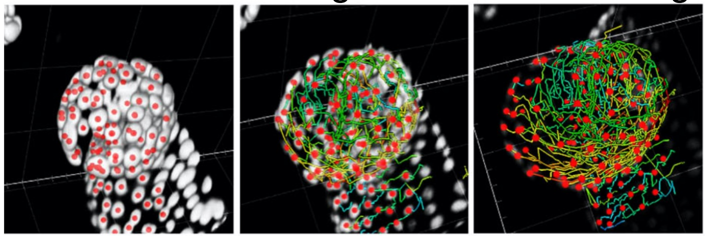
4D linking



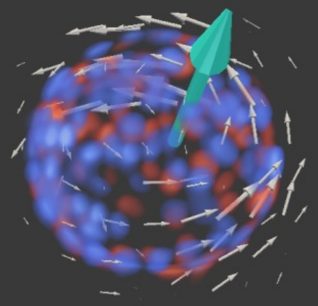


3D linking

Segmentation & tracking



movement

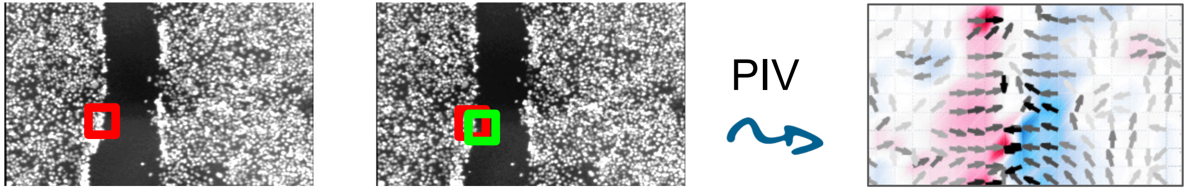


& shape analysis

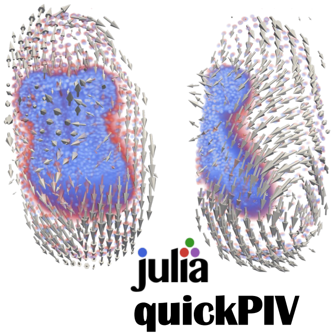
Movement Analysis – 2D/3D PIV [M. Pereyra]

Particle image velocimetry (PIV)

Velocity field



Cross-correlation: $$R(\Delta x, \Delta y) = \sum_{k=0}^{K-1} \sum_{l=0}^{L-1} I_1^{i,j}(k,l) \cdot I_2^{i,j}(k+\Delta x, l+\Delta y)$$



Currently **fastest 3D PIV** package available

	C++	OpenPIV (Python)	quickPIV
2D	63 ms	160.81 ms	50.42 ms
3D	--	59.72 s	18.09 s

Many advantages:

- Fast, robust, reliable
- No problem with cell clusters
- No segmentation needed
- No staining needed

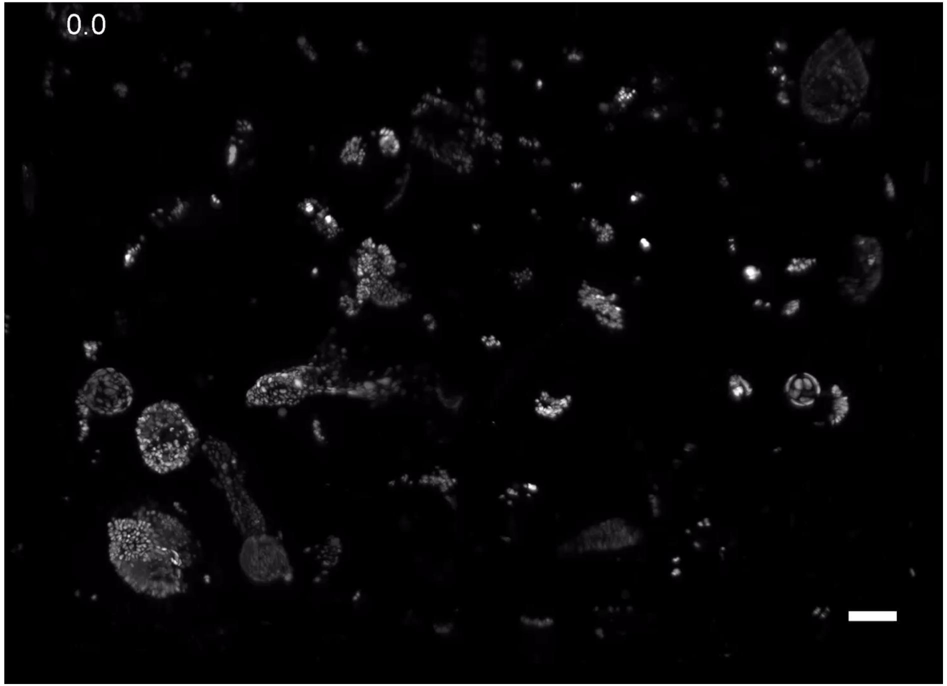
Features:

- Cross-correlation
- Peak sub-voxel approximation
- Multi-pass
- Filtering & Post-processing
- Spatial & temporal averaging
- Similarity-selective averaging
- Mappings
- Pseudo-Trajectories

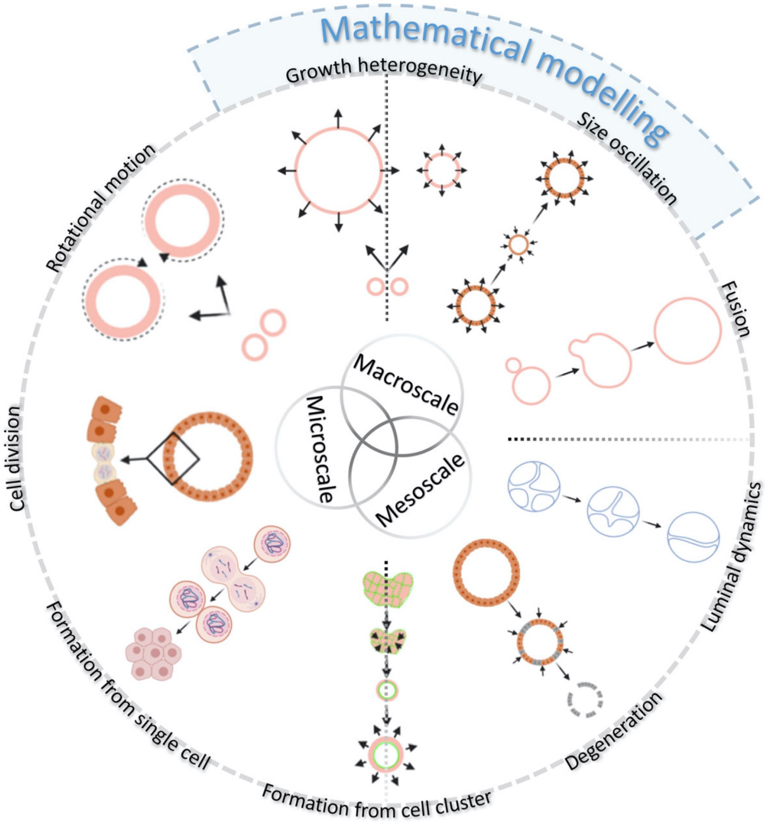
Pereyra et al., BMC Bioinformatics, 2021, Glover et al., PLoS Biol, 2017; Stichel et al., NPJSBA, 2017; Müller et al., J Pathol, 2015

Example: Dynamics of Pancreas Organoids

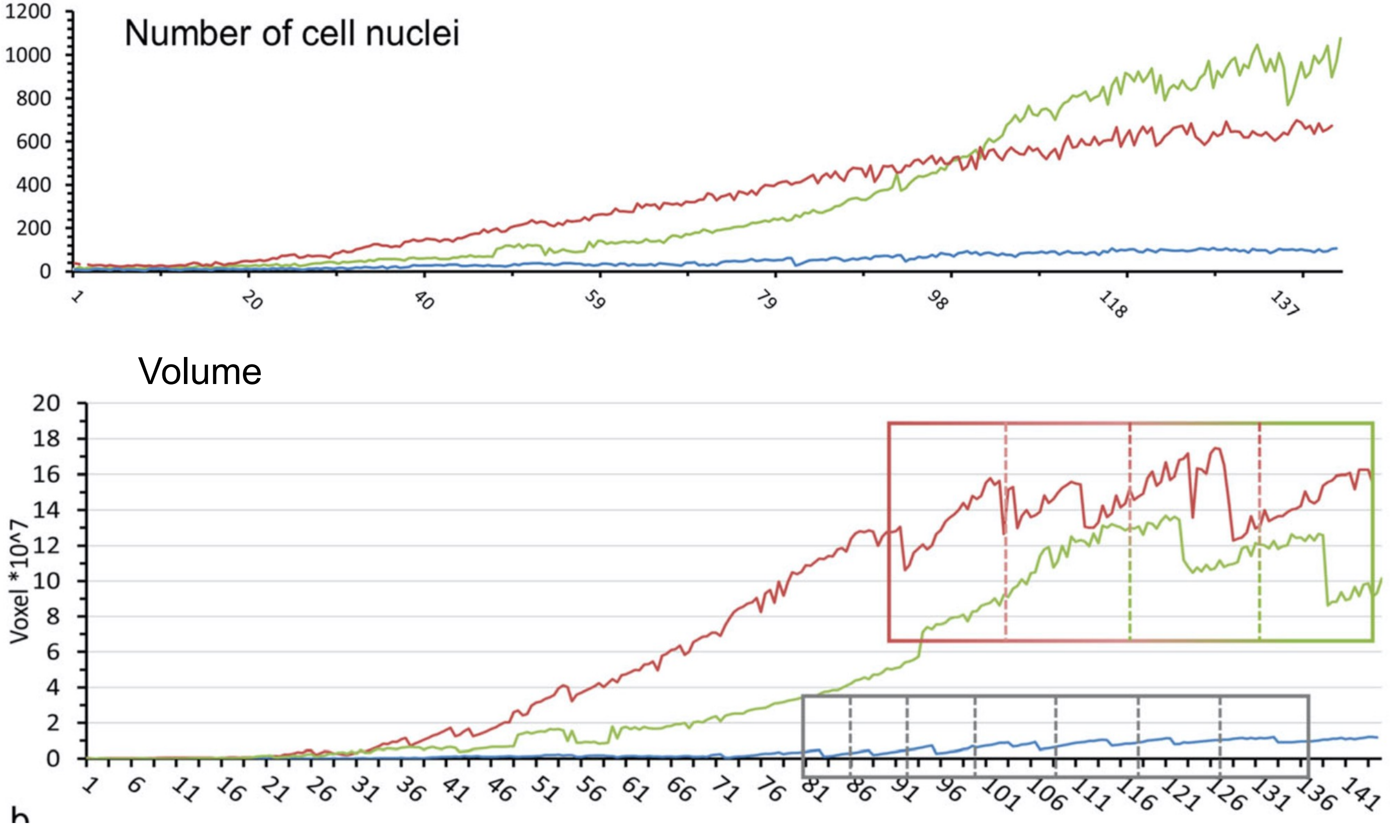
Pancreas organoid dynamics [T. Liebisch, M. Kurtz]



Pancreas Organoid Dynamics, Stelzer Lab



Size oszillations [T. Liebisch, M. Kurtz]



Scaling law for dependence of size oscillation events on cell division dynamics

Volume-area relationship for spherical objects: $V \sim A^{3/2}$

Production rate of substances is proportional to cell number: $\dot{n}(t) \sim N(t)$

Osmotic pressure depens on concentration and volume: $\Pi = c \times i_{\nu H} \times R \times T = \frac{n}{V} \times i_{\nu H} \times R \times T \sim \frac{n}{V}$

Surface is proportional to cell count, i.e., $N(t) \sim A(t)$, therefore $n \sim \int A(t)$

This yields $\Pi \sim \frac{\int A(t)}{A(t)^{3/2}}$

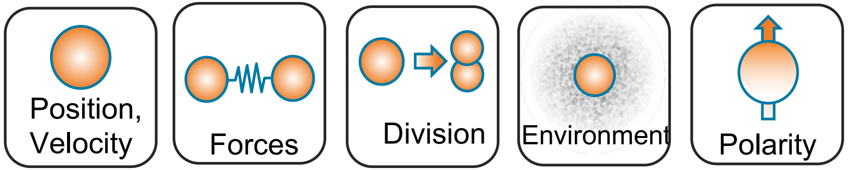
Rupture happens if pressure increases. Constant pressure requires $\frac{\int A(t)}{A(t)^{3/2}} = \text{const.}$

This is given when $A(t) \sim t^2$

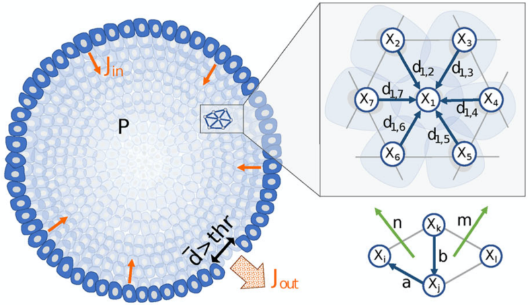
Constant cell division rate ⇨ exponential increase ⇨ faster than quadratic growth ⇨ expect no ruptures

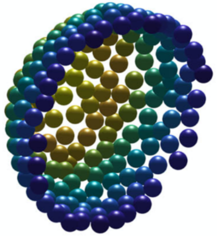
Linear increase in cell number for division rate decreasing as $1/t$ ⇨ expect ruptures

Agent-based model reproduces organoid dynamics [T. Liebisch, M. Kurtz, L. Ramirez]

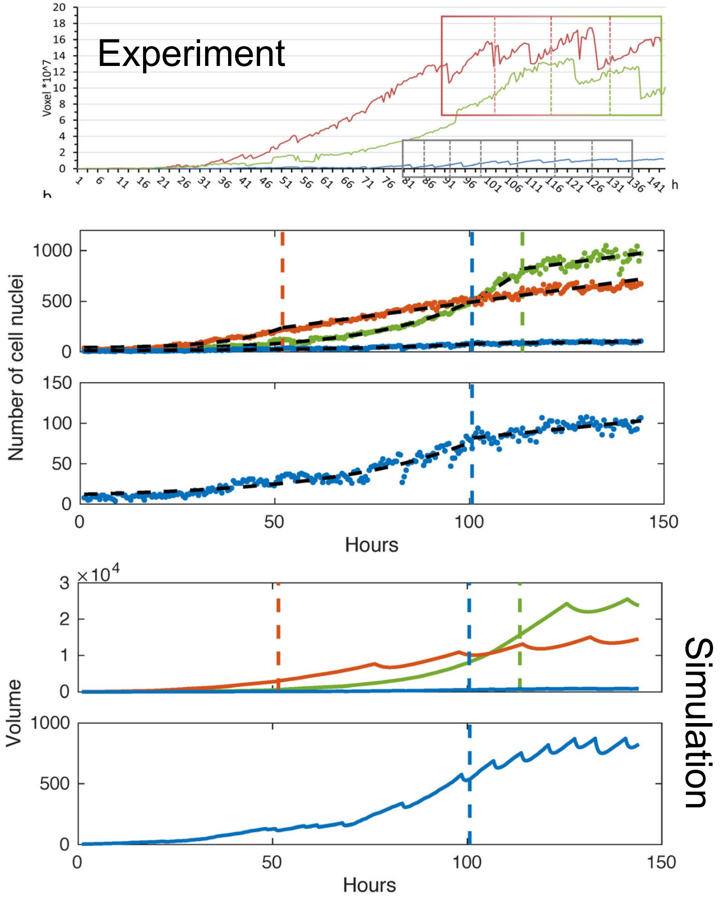


- F includes cell polarity or bending potential
- cell division included
- dynamics of secretion of osmotically active substance $\frac{dn}{dt} = NJ_{in} - J_{out}n$
- osmotic pressure $\Pi = \frac{n}{V} \cdot i_{vH} \cdot R \cdot T$

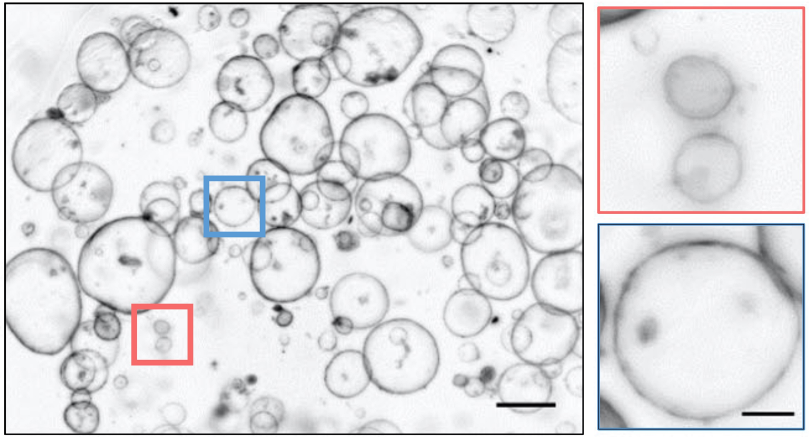


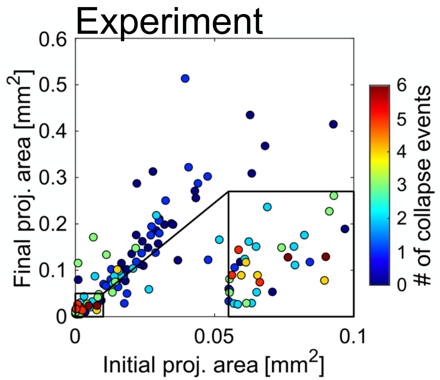


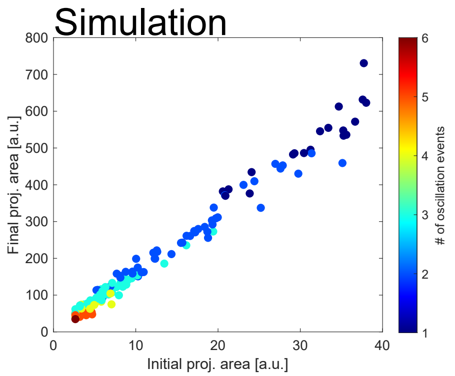
Agent-based model confirms scaling law



Further validation using bright-field pipeline

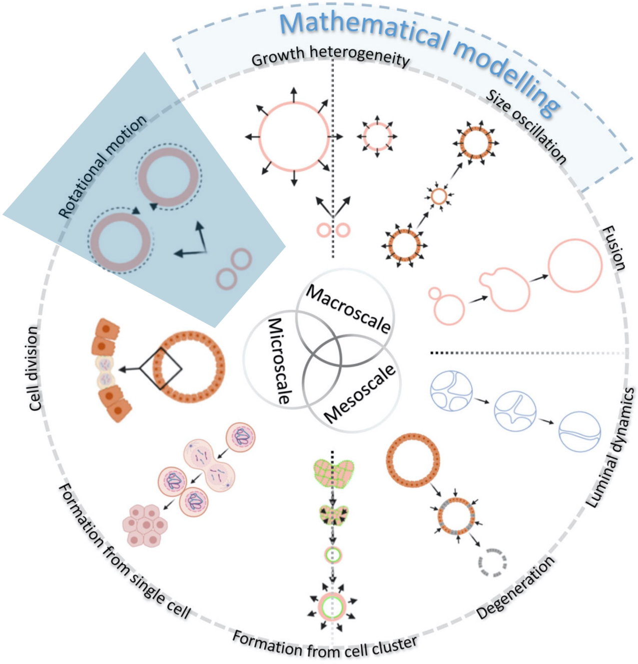






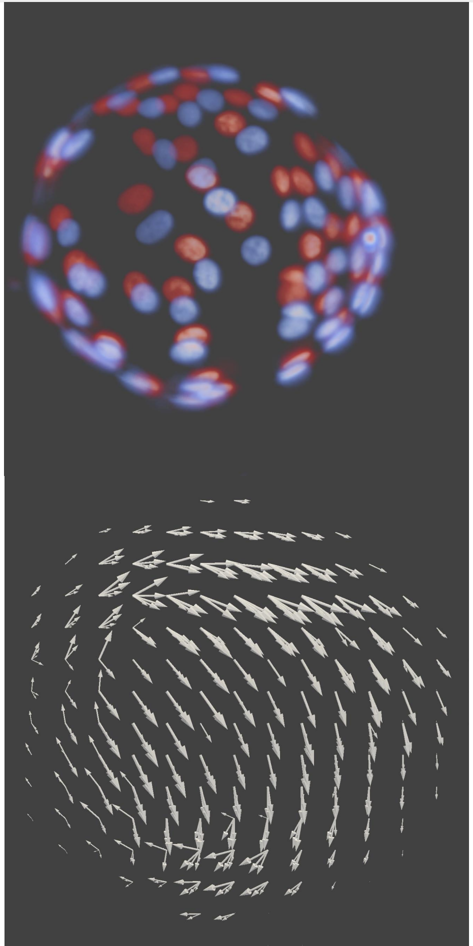
Hof et al., BMC Biology, 2021

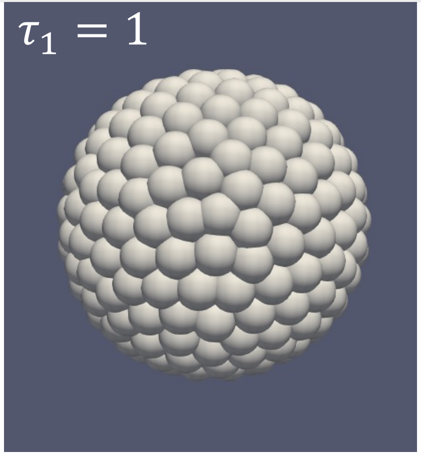
Further Dynamics: Rotation

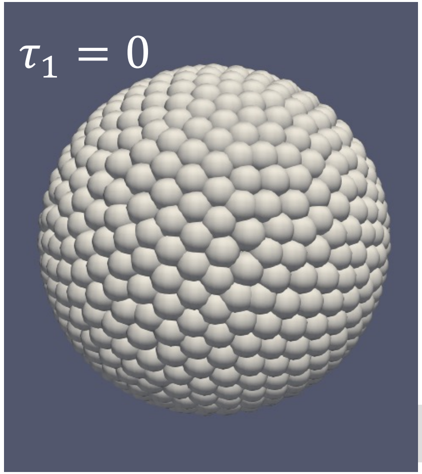


- active migration / acceleration

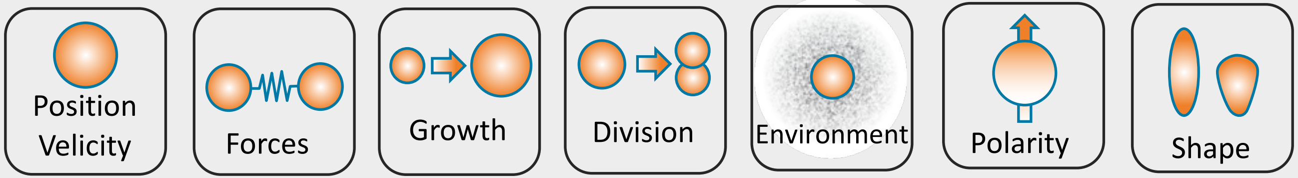
$$\frac{dv}{dt} = \sum A_0 F + \frac{1}{\tau}(v_0 - v)$$

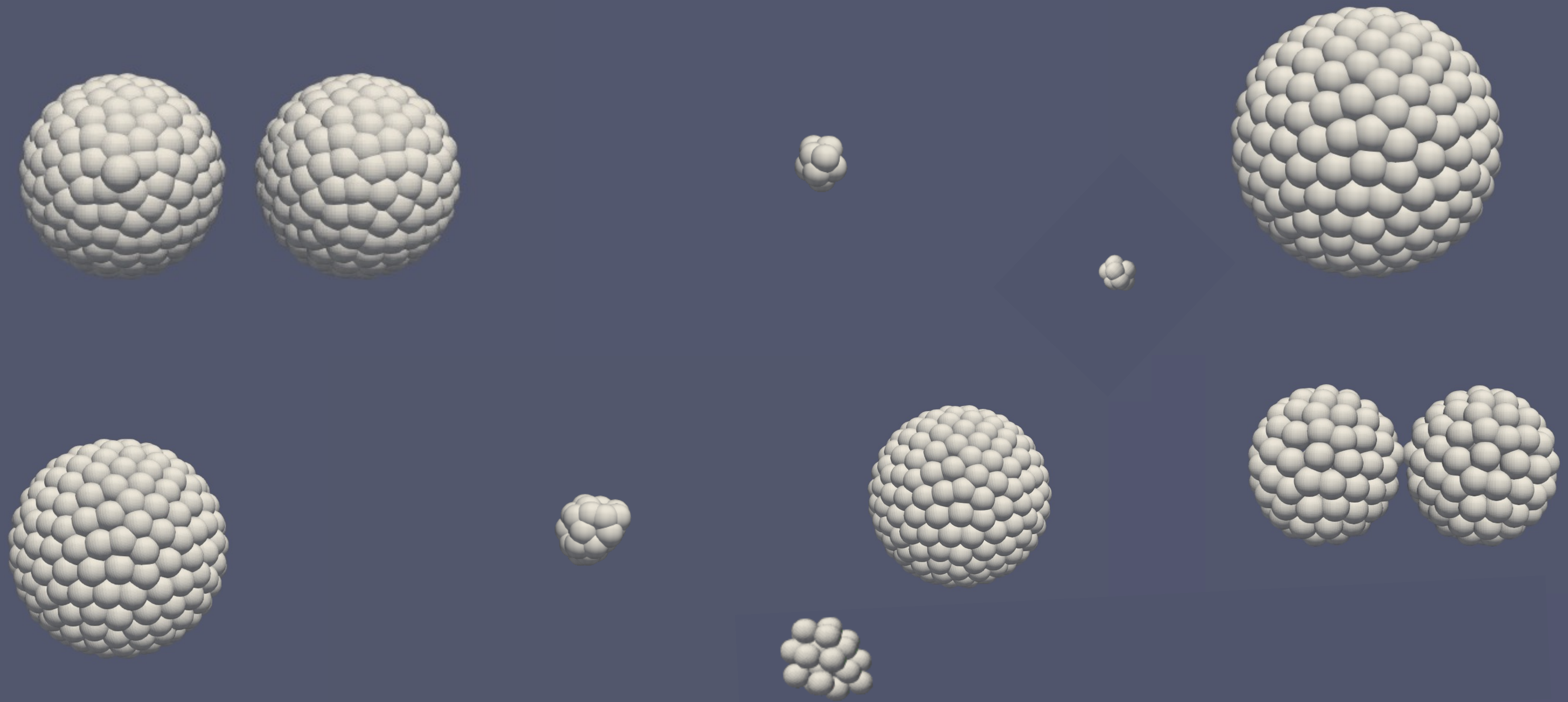




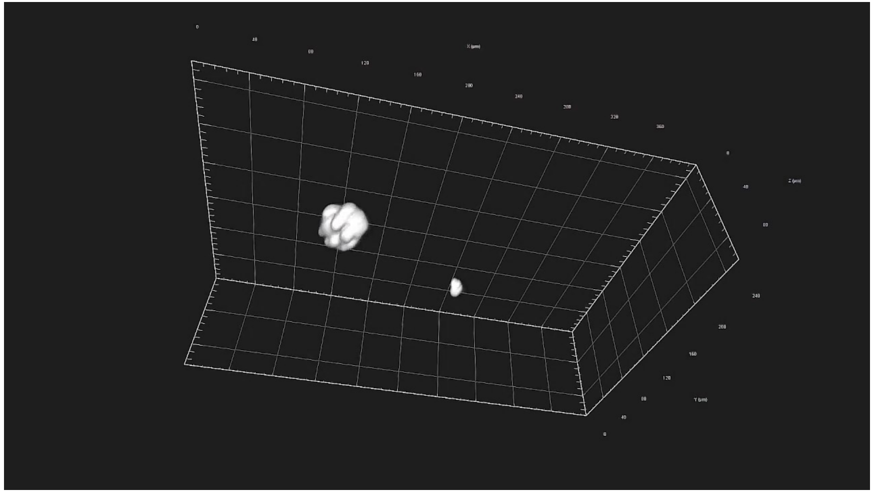


(Almost) Full Virtual System



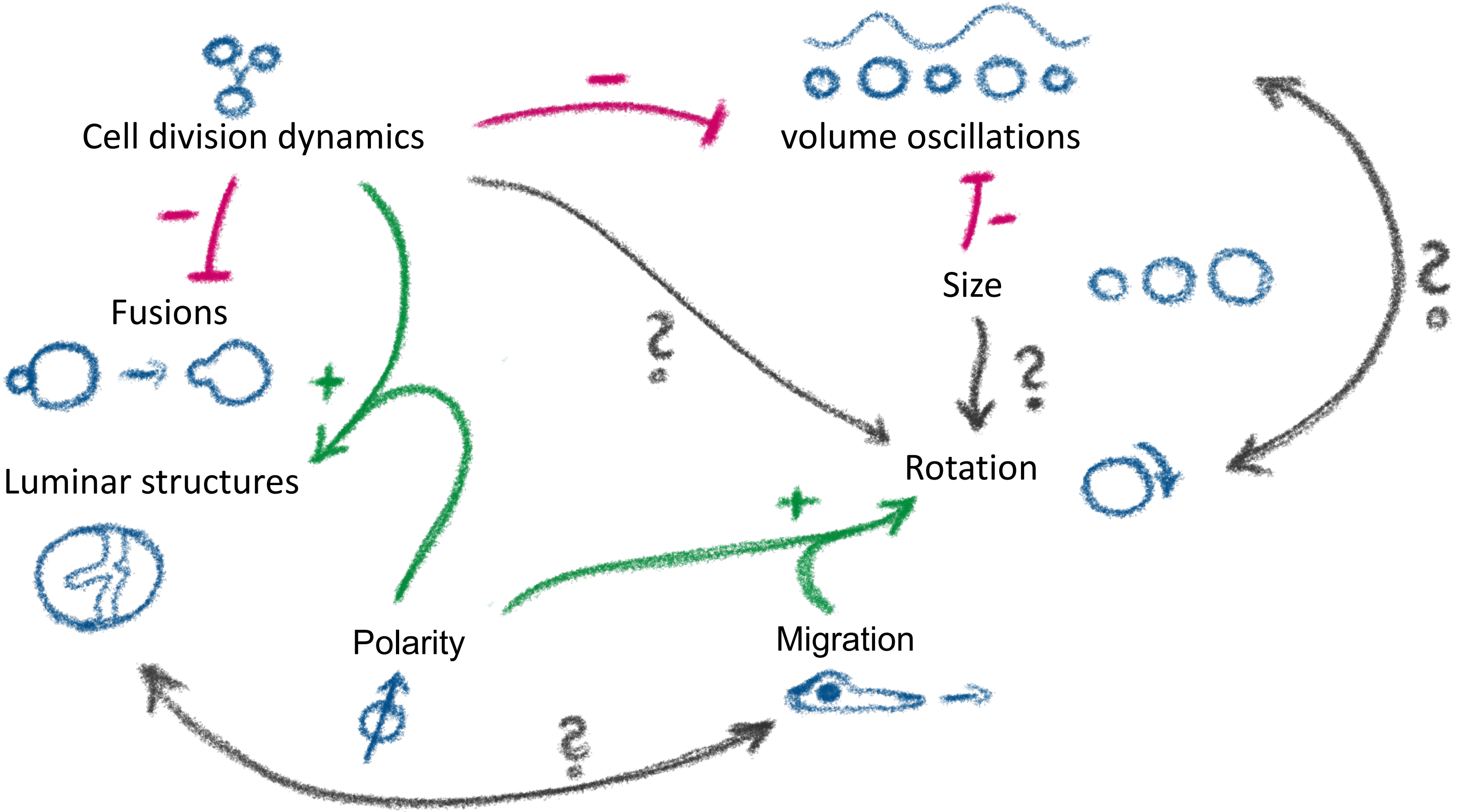


Migration



Hof et al., BMC Biology, 2021

What do we learn from these simulations?



Summary / Outlook / Challenges

Take Home message:

Agent-based models are useful in determining regulatory processes and biophysical principles underlying collective phenomena in multicellular systems.

Efficiency / Scaling:

Stochastic simulations are computationally expensive
Current efforts: increase parallelization / GPU implementation

Parameter estimation:

Requires summary statistics / large number simulations for every parameter set
Current efforts: explore AI approaches (simulation-based inference)
Vision: direct parameter estimation using original data (no summary statistics)

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DYNAMEM

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