Diversity of shapes

Silas Boye Nissen & Ala Trusina & Kim Sneppen

How do complex shapes form?

All organs have an inside-outside and a given flow direction

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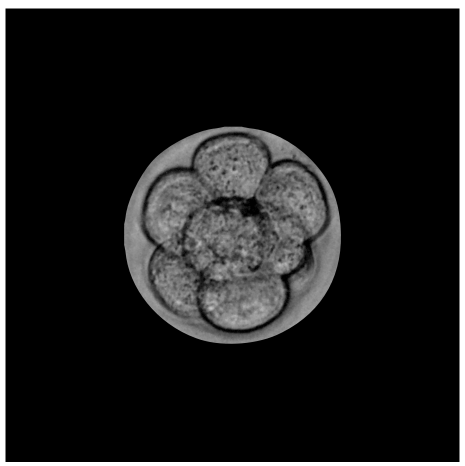
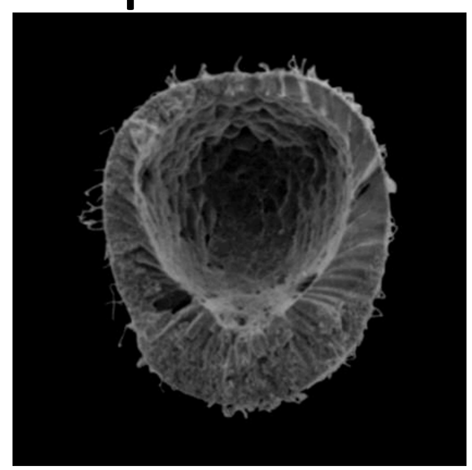
General pattern in organogenesis?

Two symmetry breaking events:

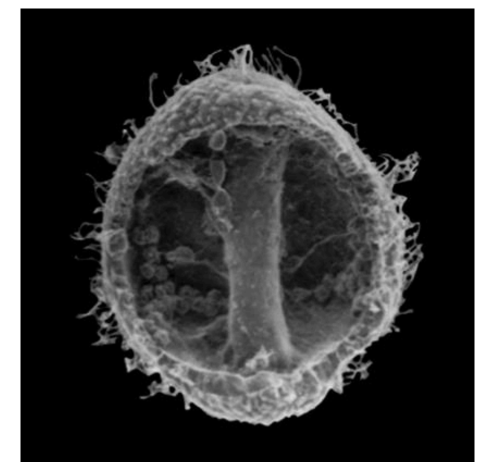
Globular



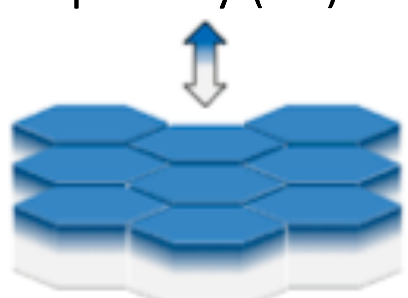
Spherical



Axial



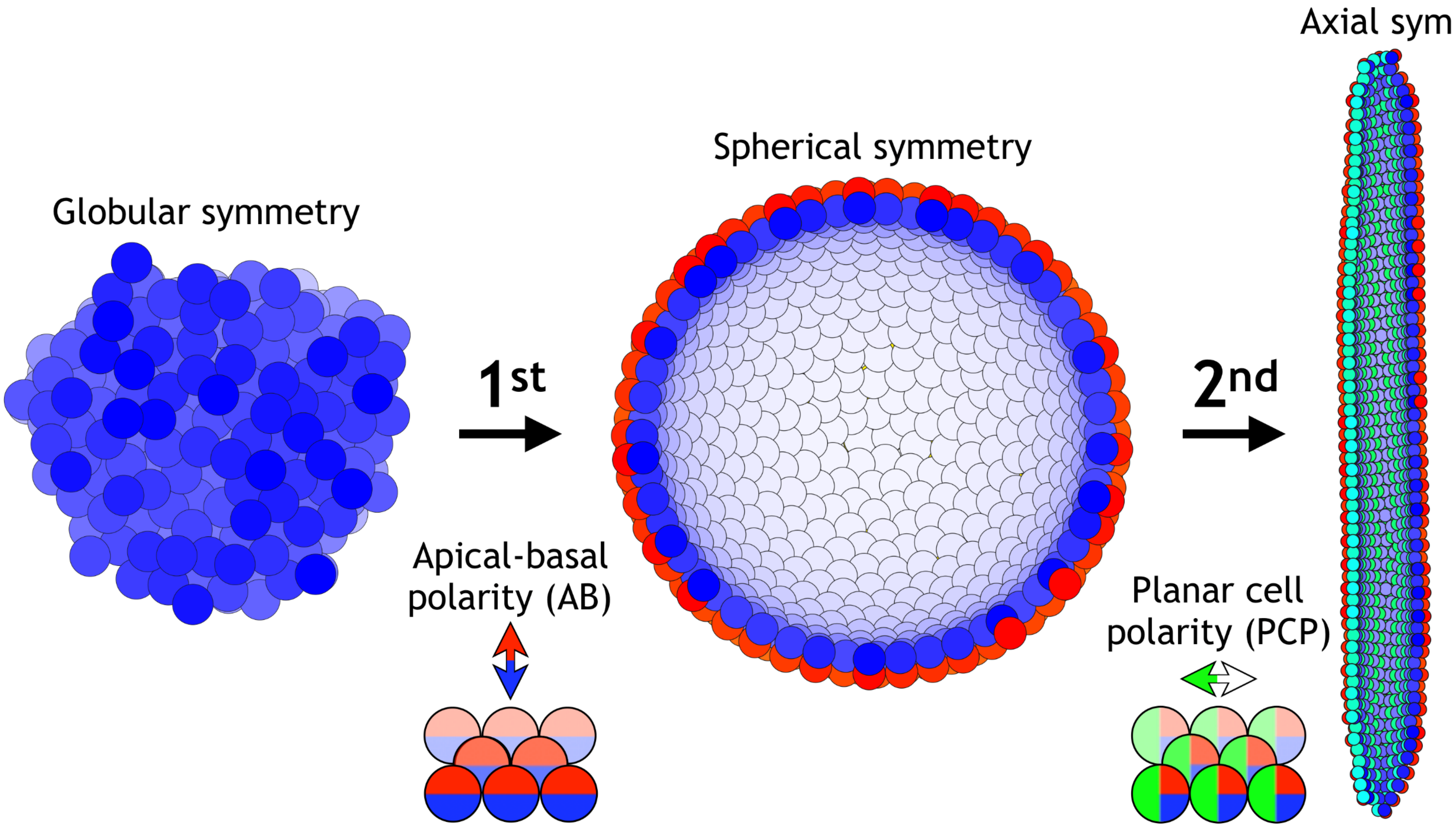
Apical basal polarity (AB)



Planar cell polarity (PCP)

Is this sufficient for organogenesis?

Symmetry breaking events in Life:



Planes (spheres) respectively Tubes (torus)

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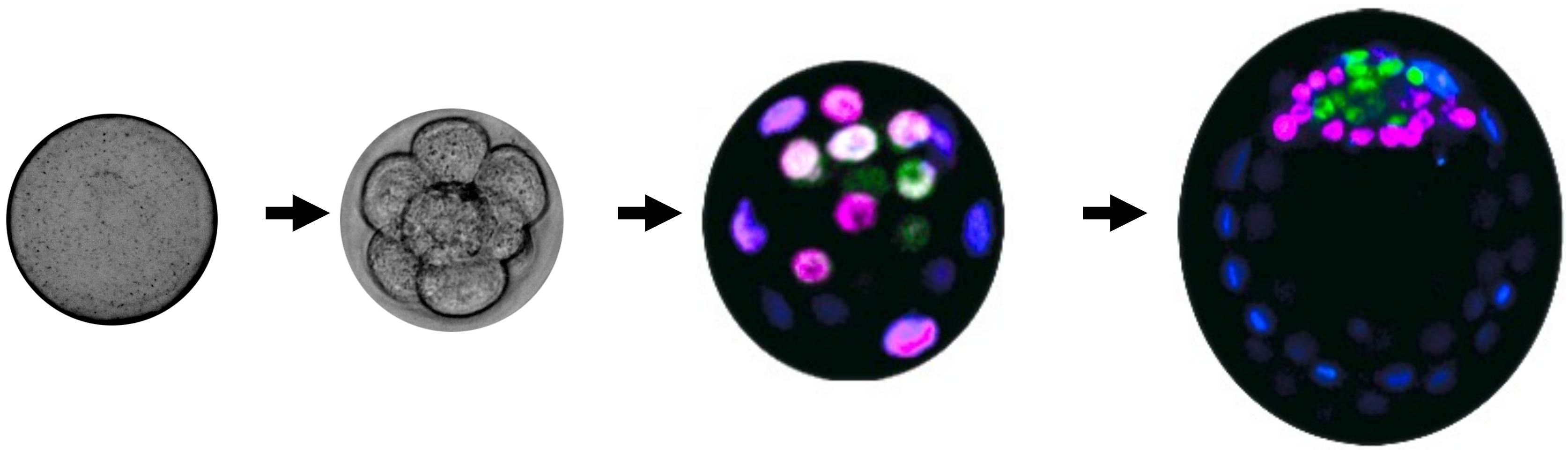
1) Formation of Blastocyst



Fertilizati
on

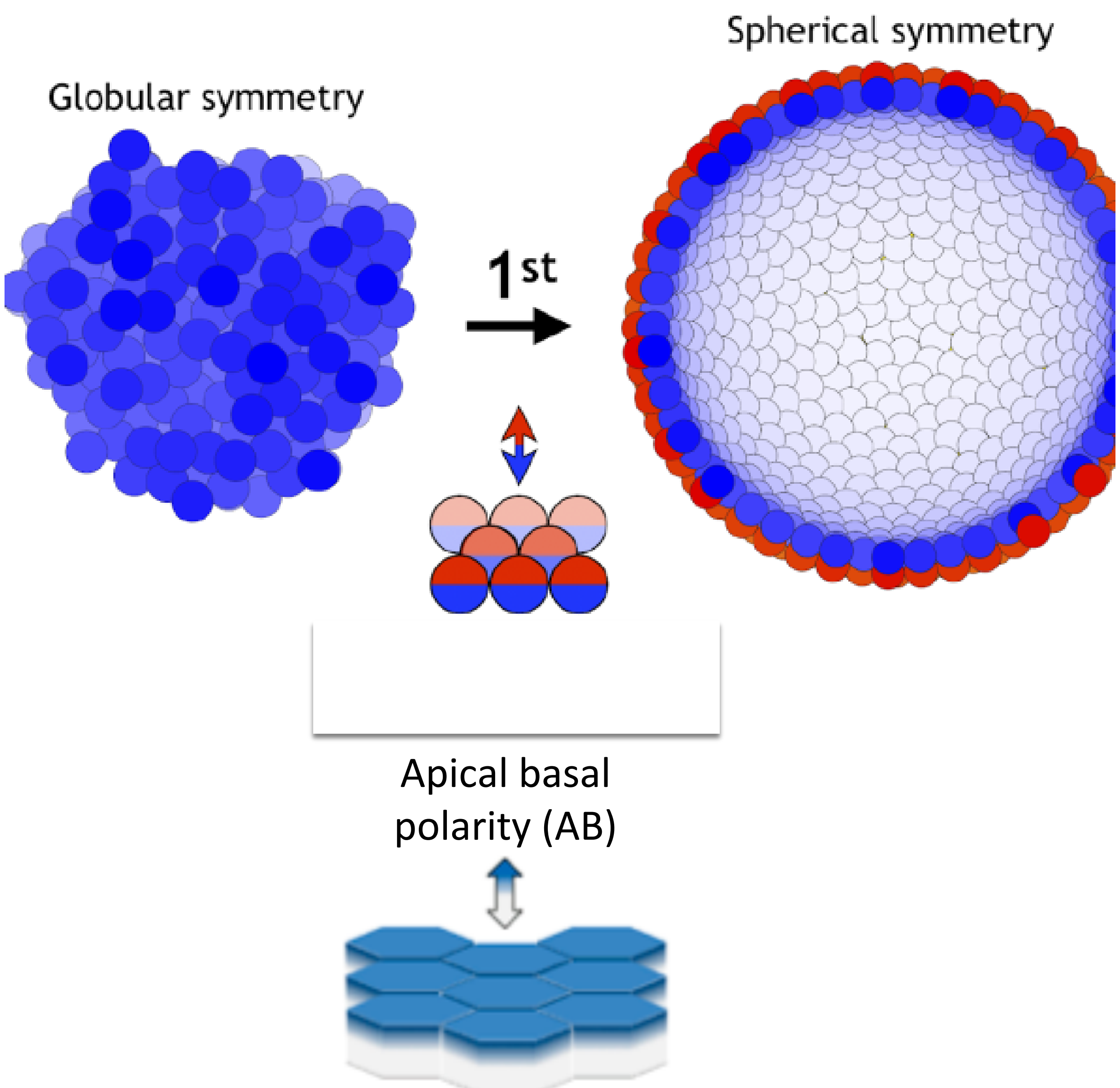
Day
2.5

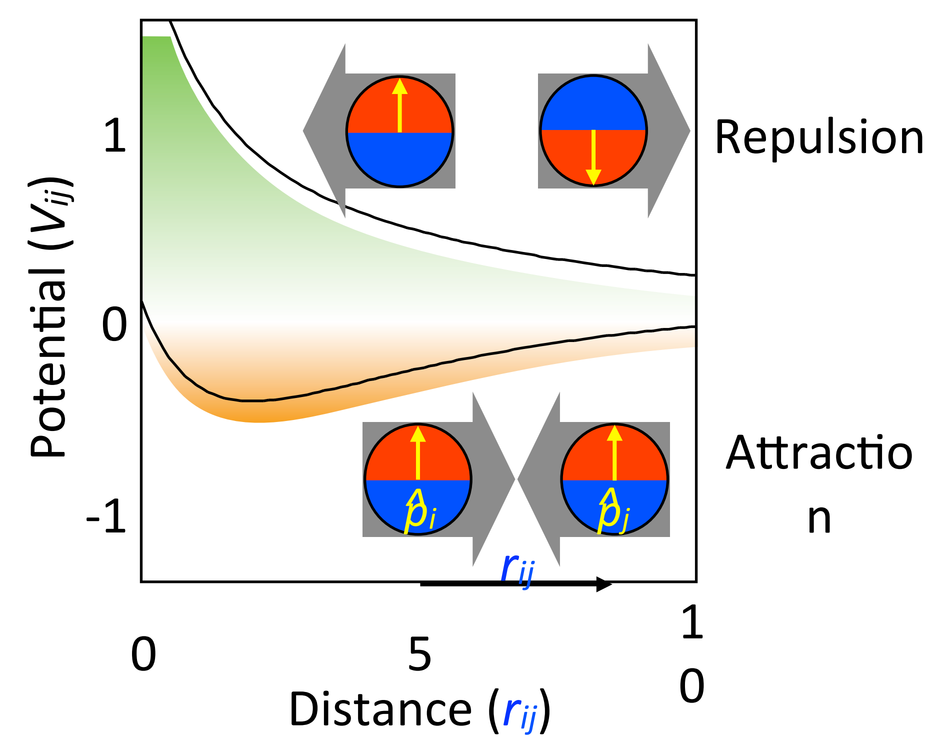
Day
3.5

Day
4.5

Nissen et al. (2017) *PLoS Biol*

AB polarity (sheets):





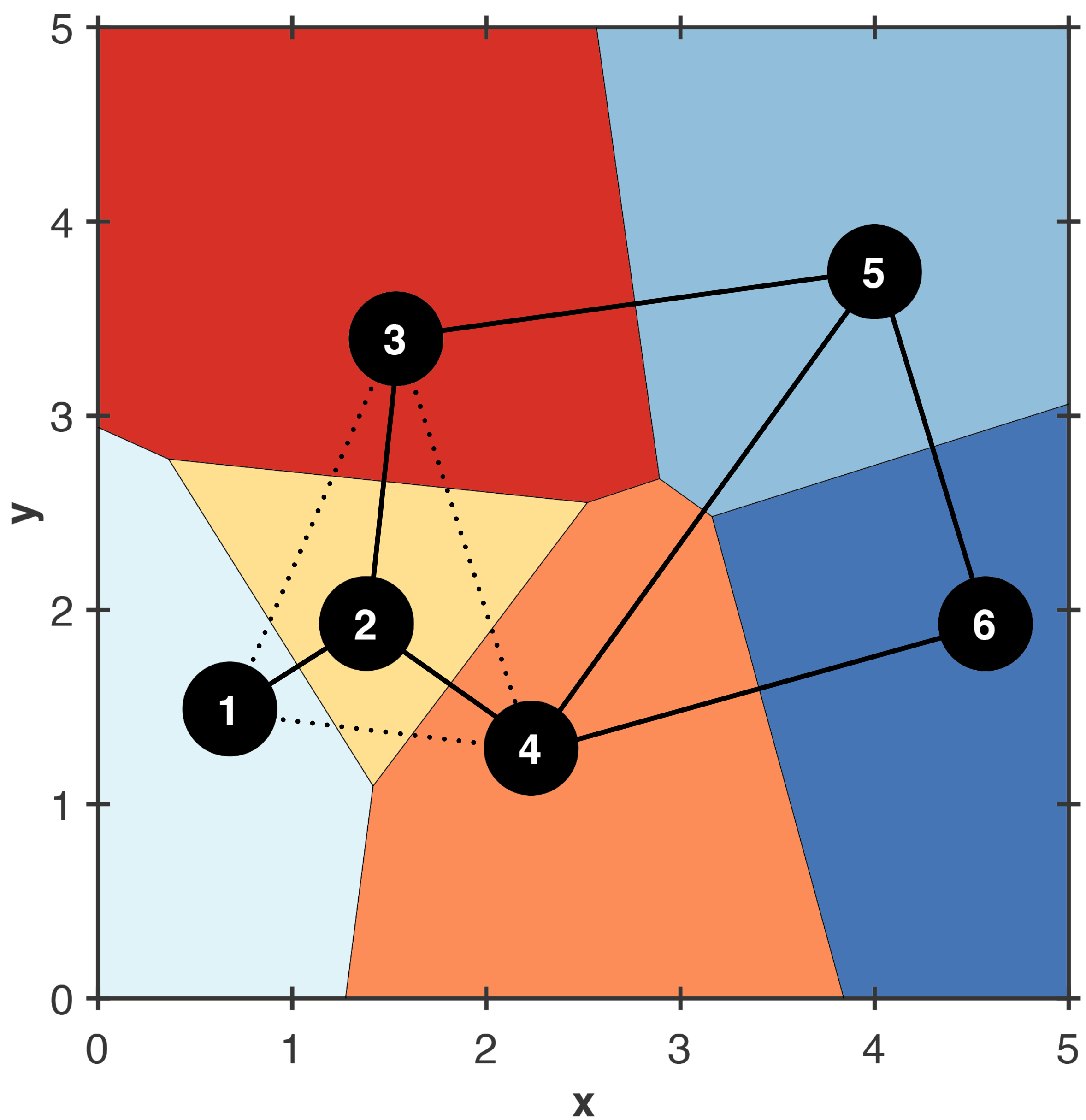
Epithelial sheet

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

$$V = \exp(-r_{ij}) - S1 * \exp(-r_{ij}/5)$$

Interacting neighbors

Who interact?



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

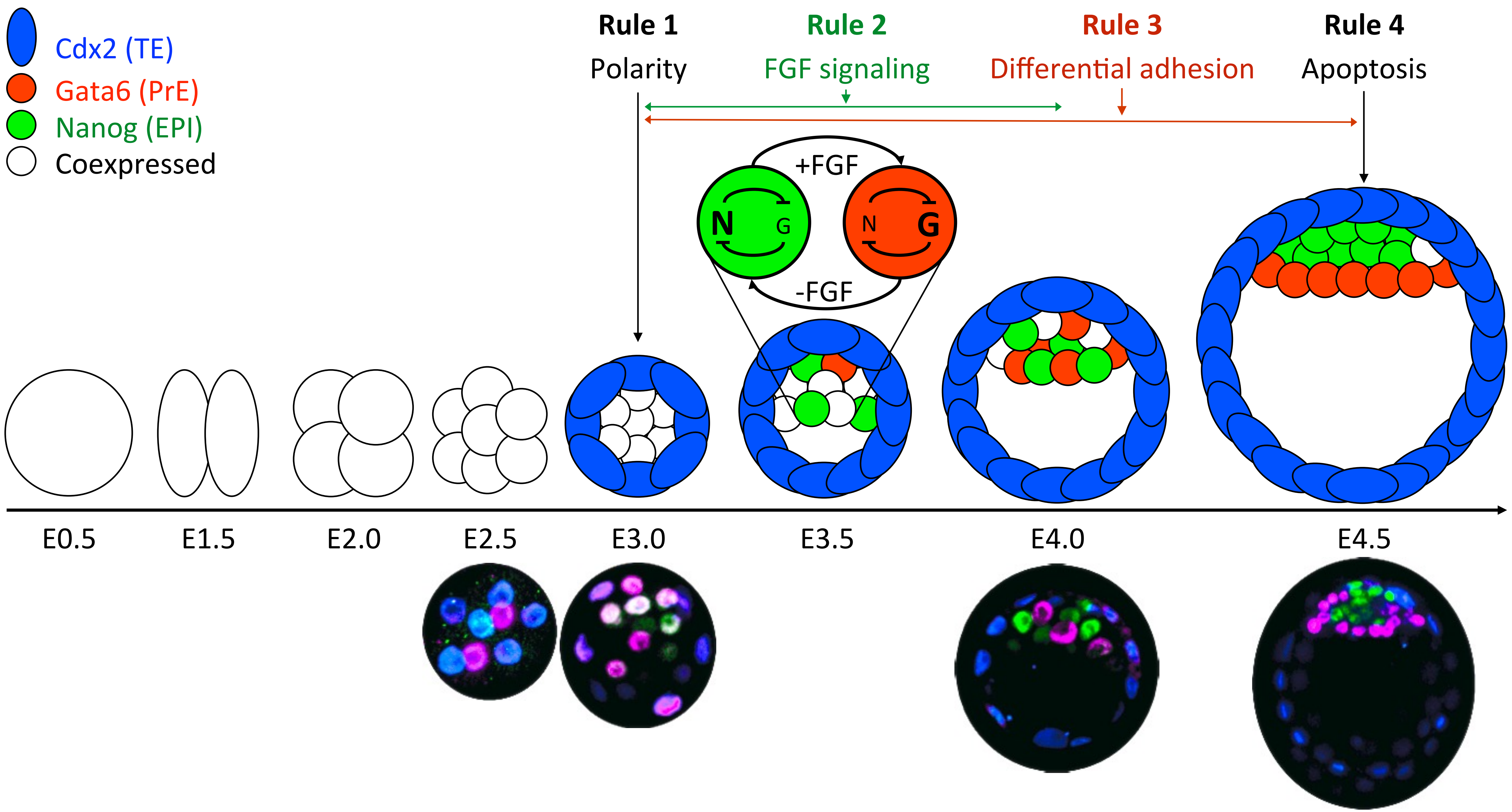
$$\frac{d\vec{r}_i}{dt} = -\frac{dV_i}{d\vec{r}_i} + \eta$$

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

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

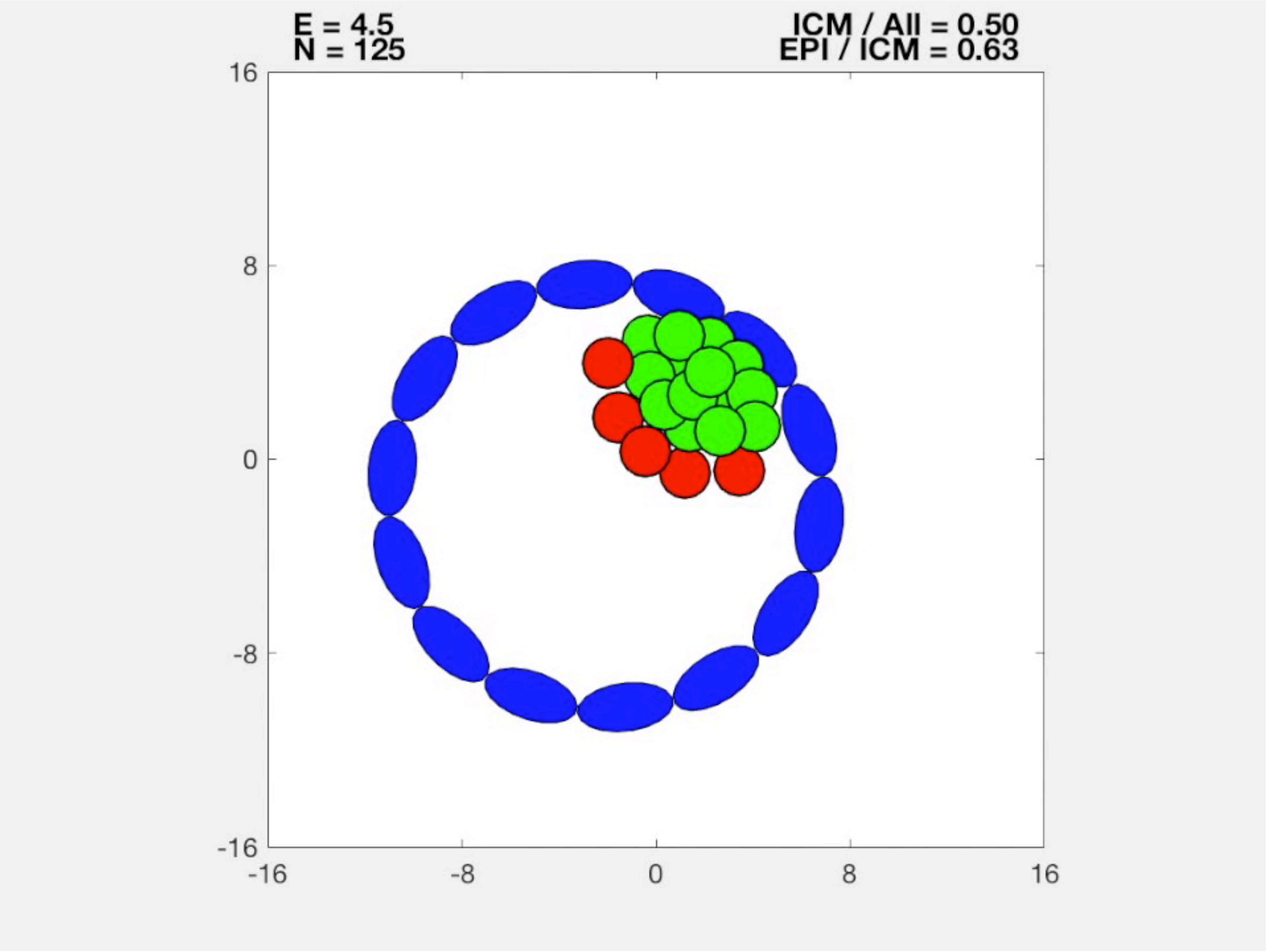
Solid lines do, dashed do not

Four simple rules for early embryonic development



Nissen et al. (2017) *PLoS Biol*

Four simple rules for early embryonic development

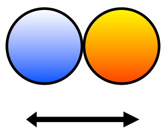


Nissen et al. (2017) *PLoS Biol*

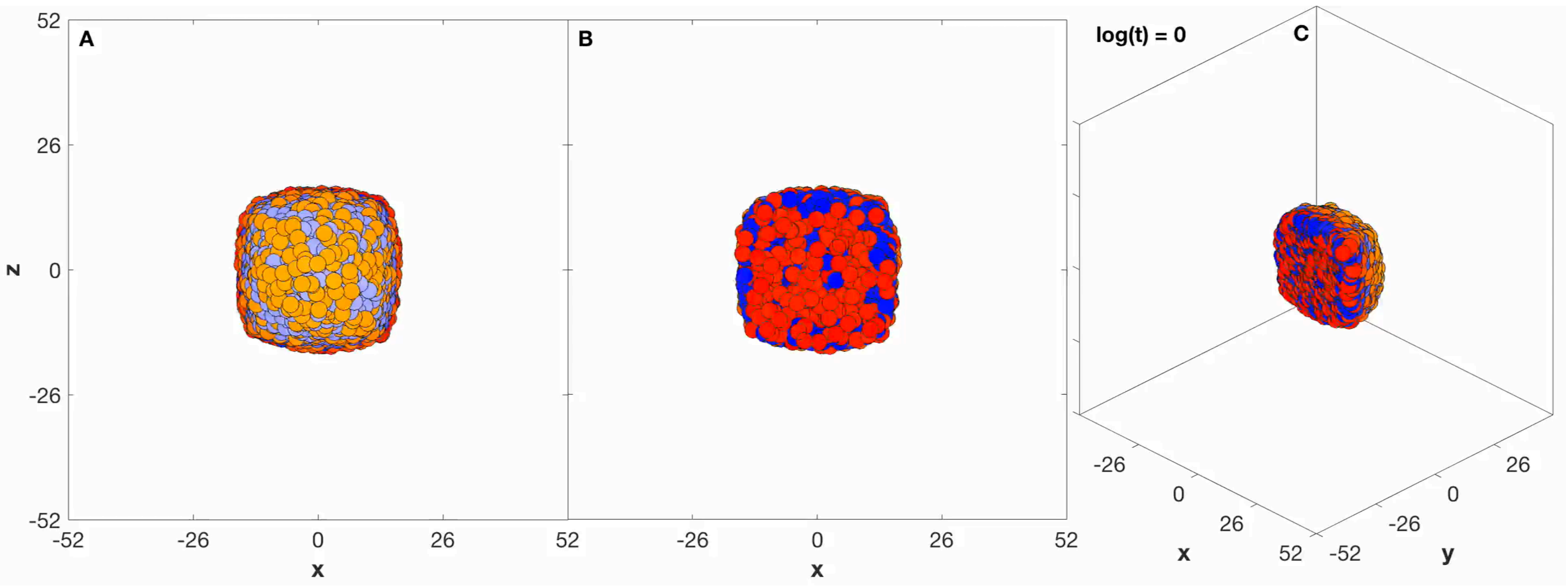
2) Playing with AB polarity….. …:

Compact aggregate unfolds

Each cell



Outside | Inside | Rotated



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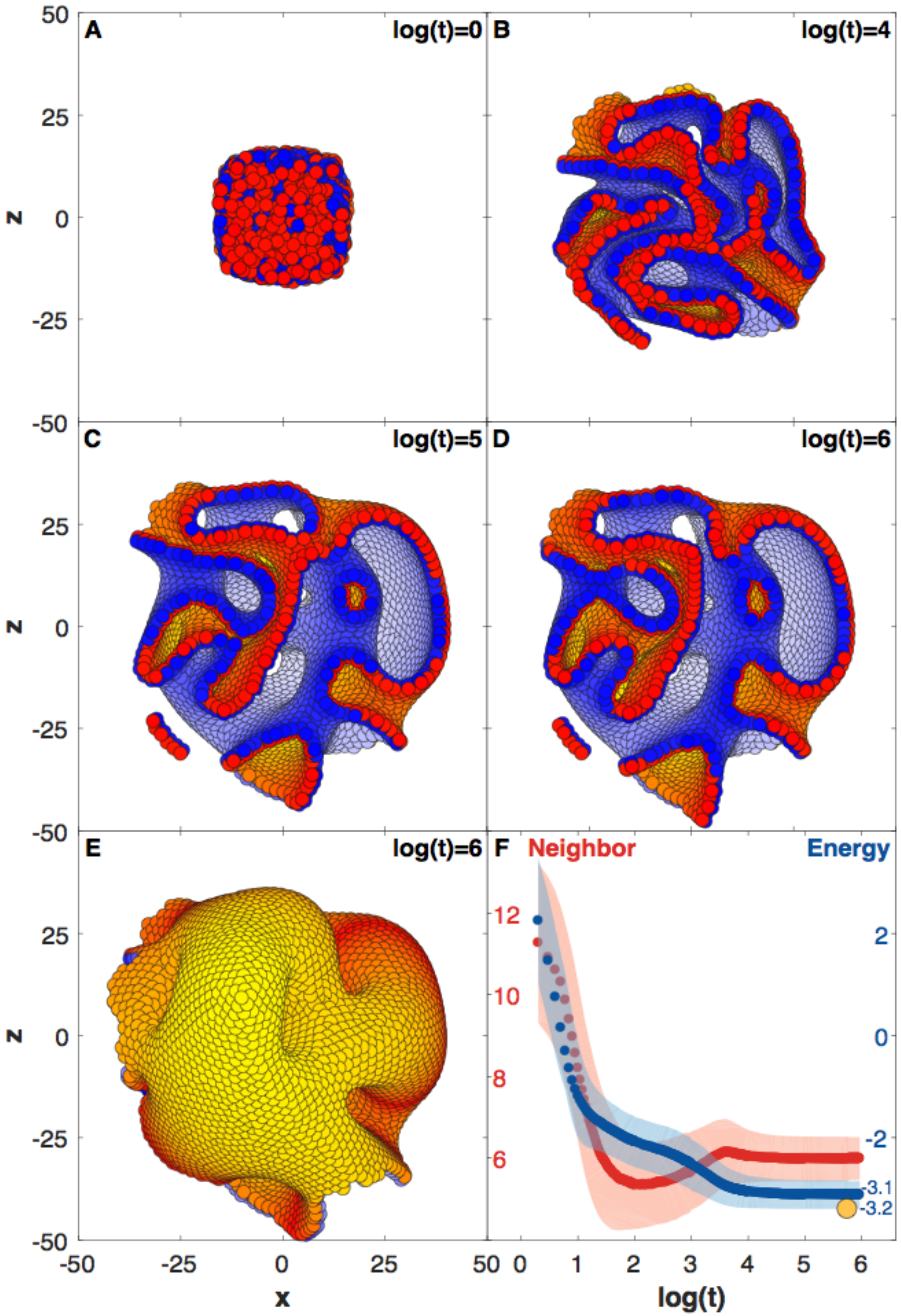
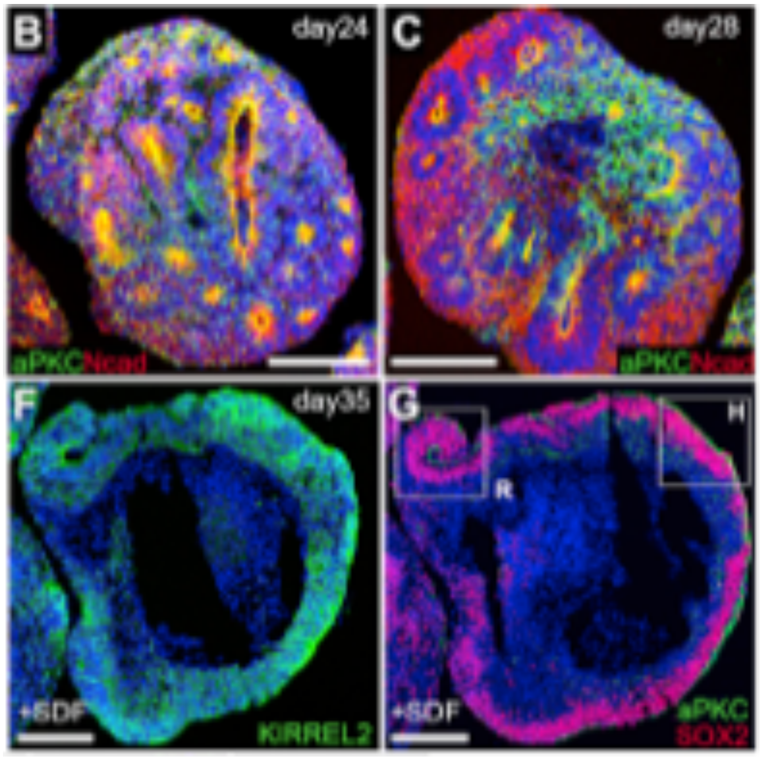
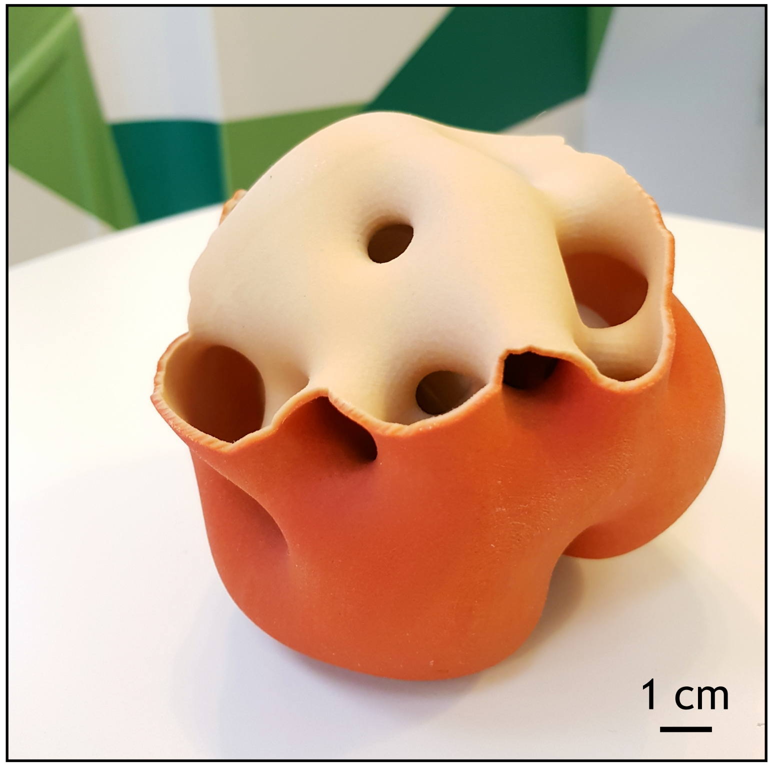
Stable complex shapes emerge





Muguruma et al. (2015)



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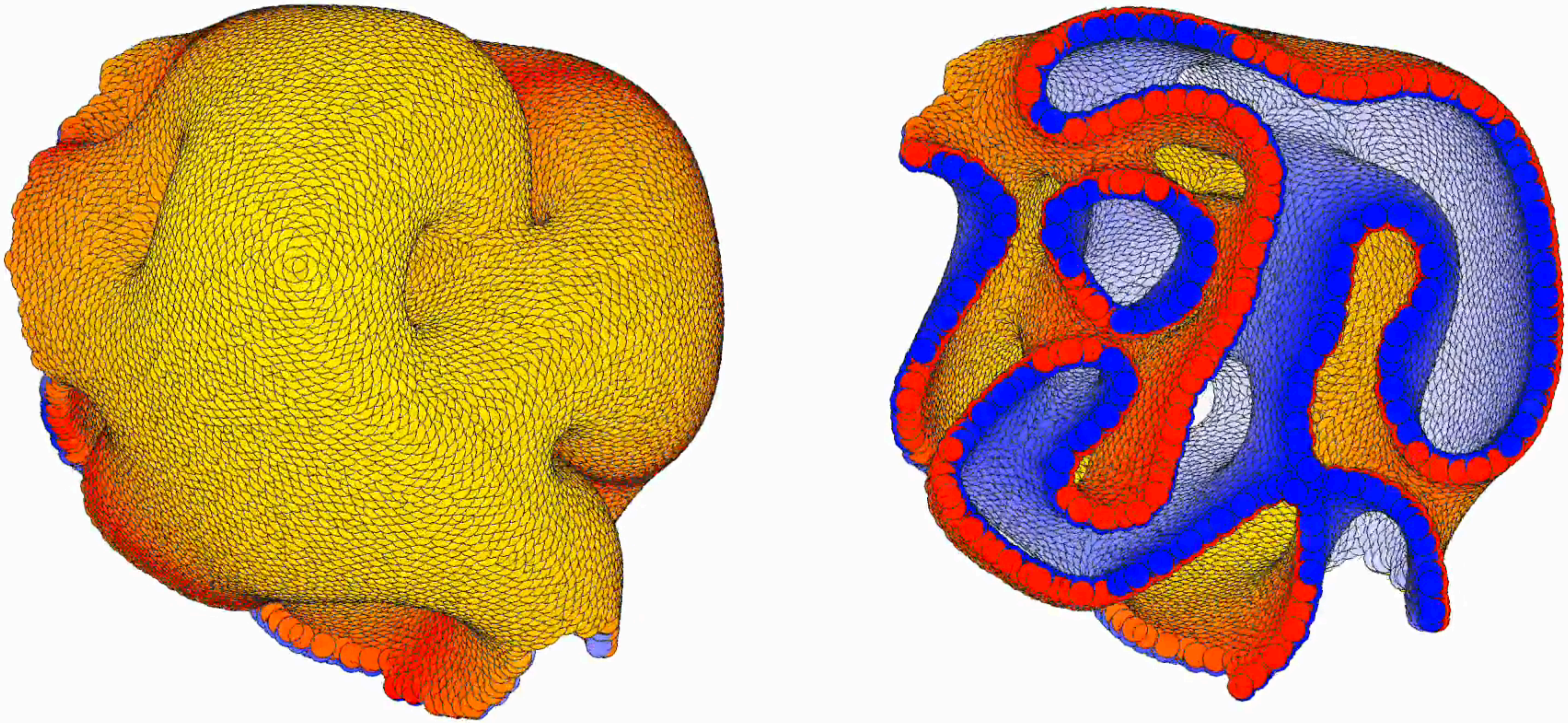
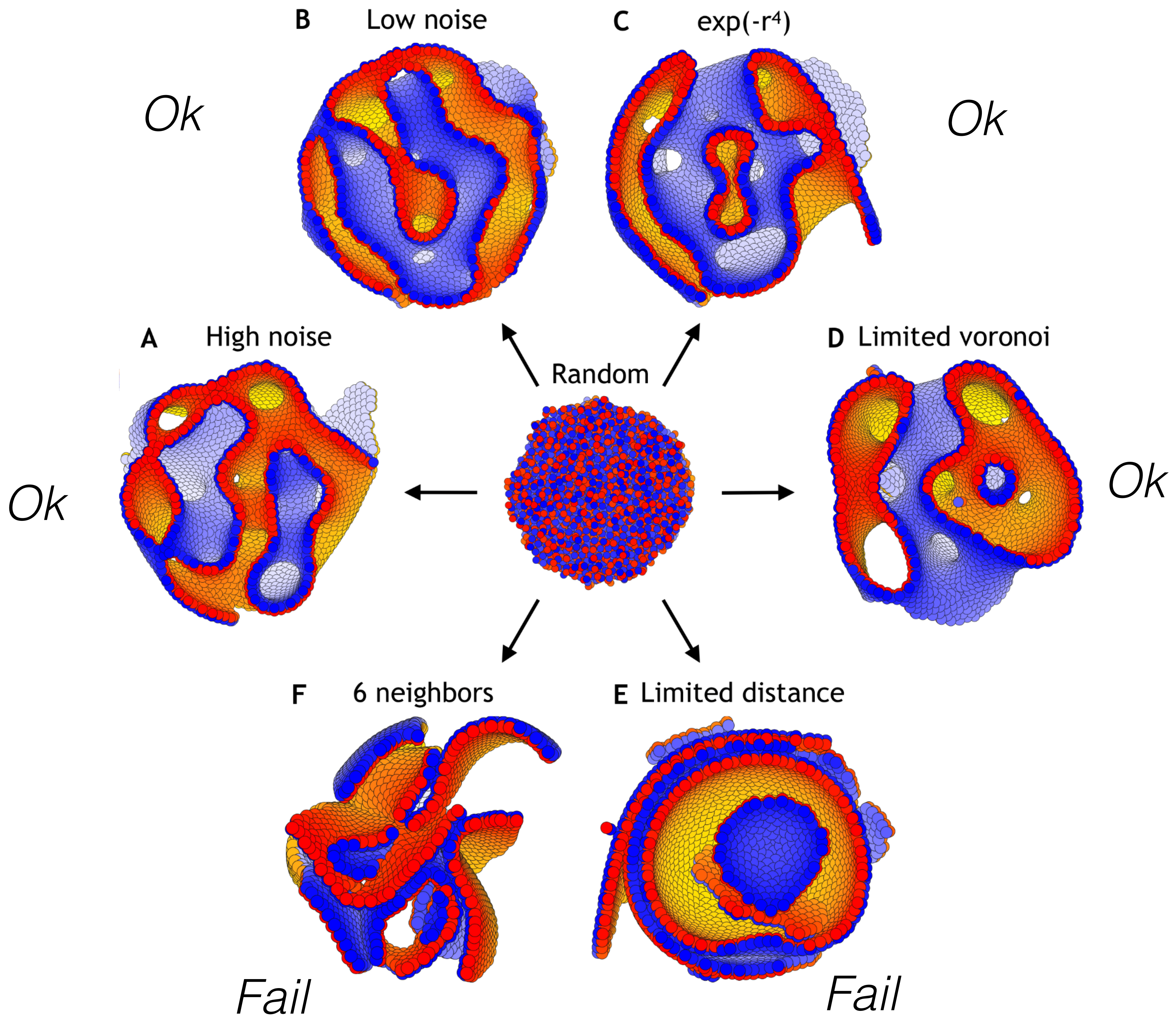
Robustness: Against growth

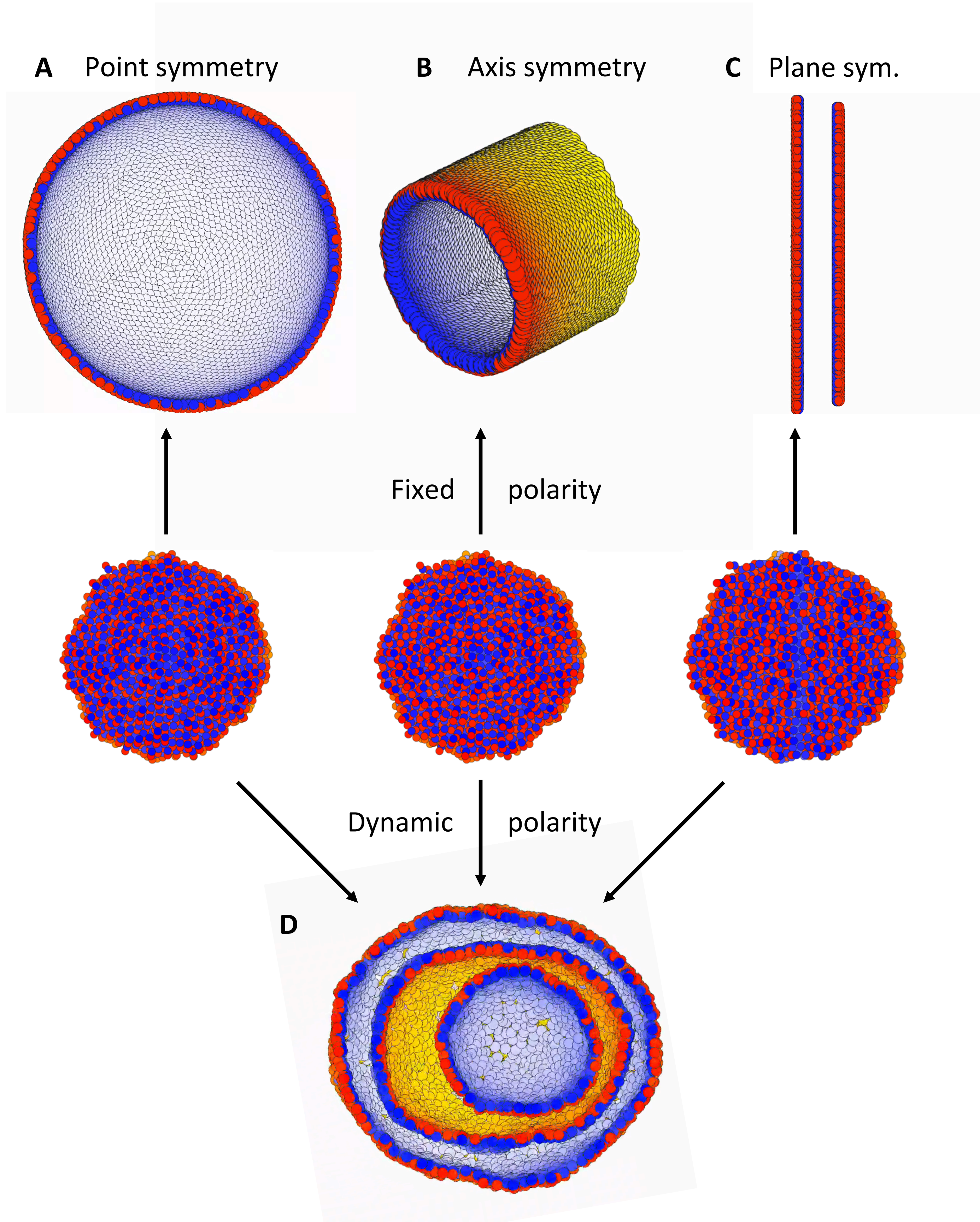
Grow from 8k cells to 25k cells



Robustness/Variants



Sensitiviity to Boundary Conditions (/constraints):

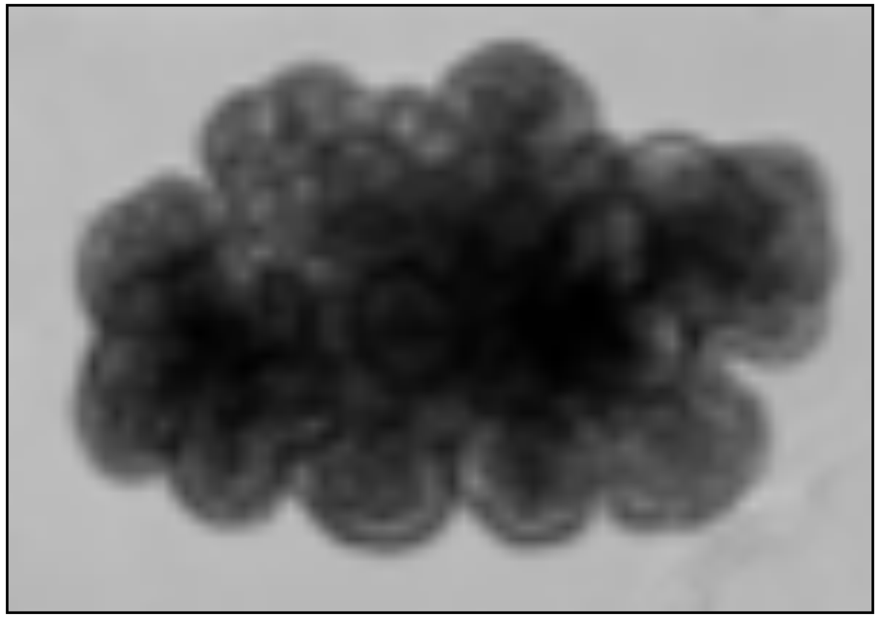


From spherical to folded organoids

If grown in medium A

all sizes are spherical

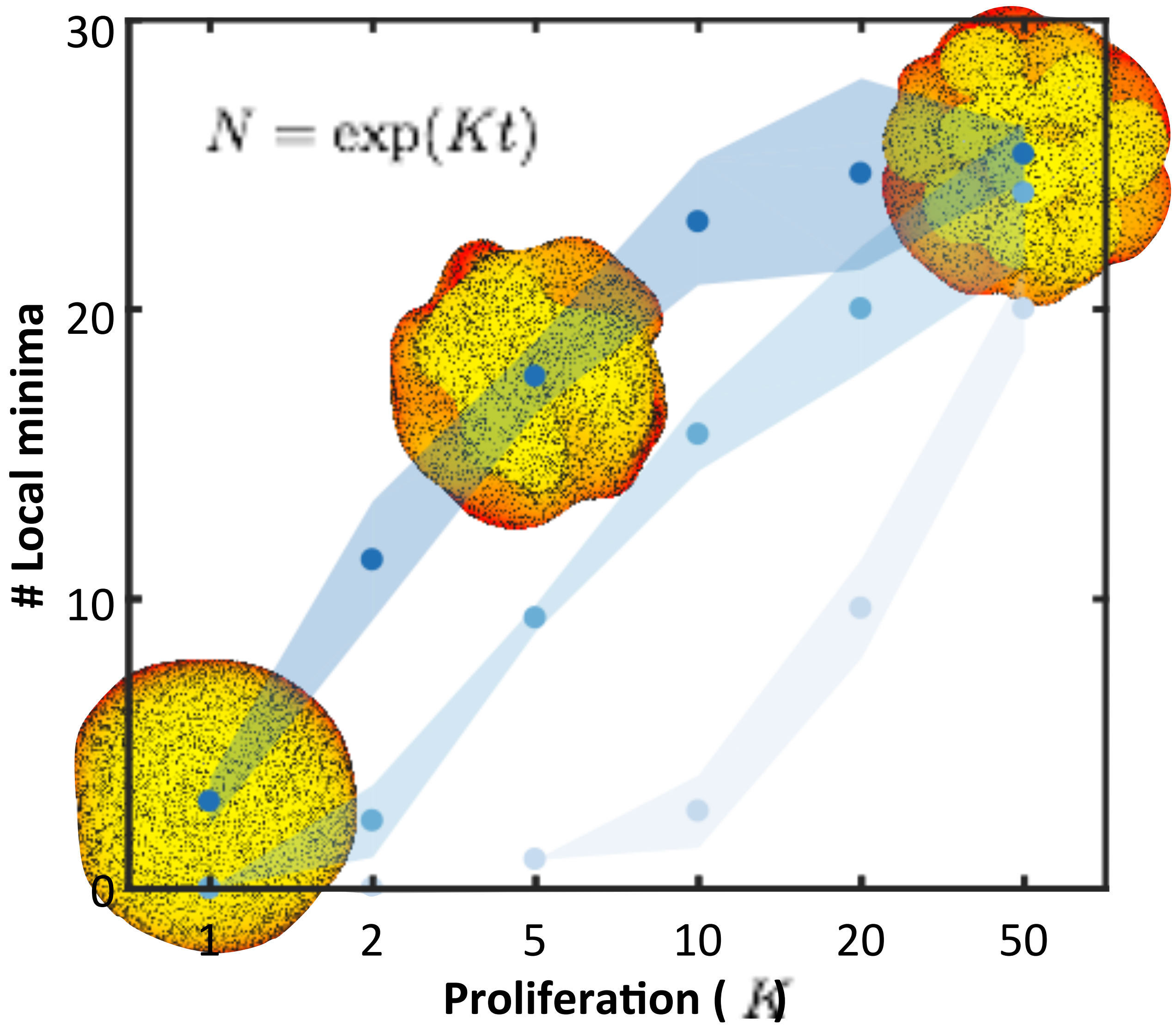
If grown in medium B

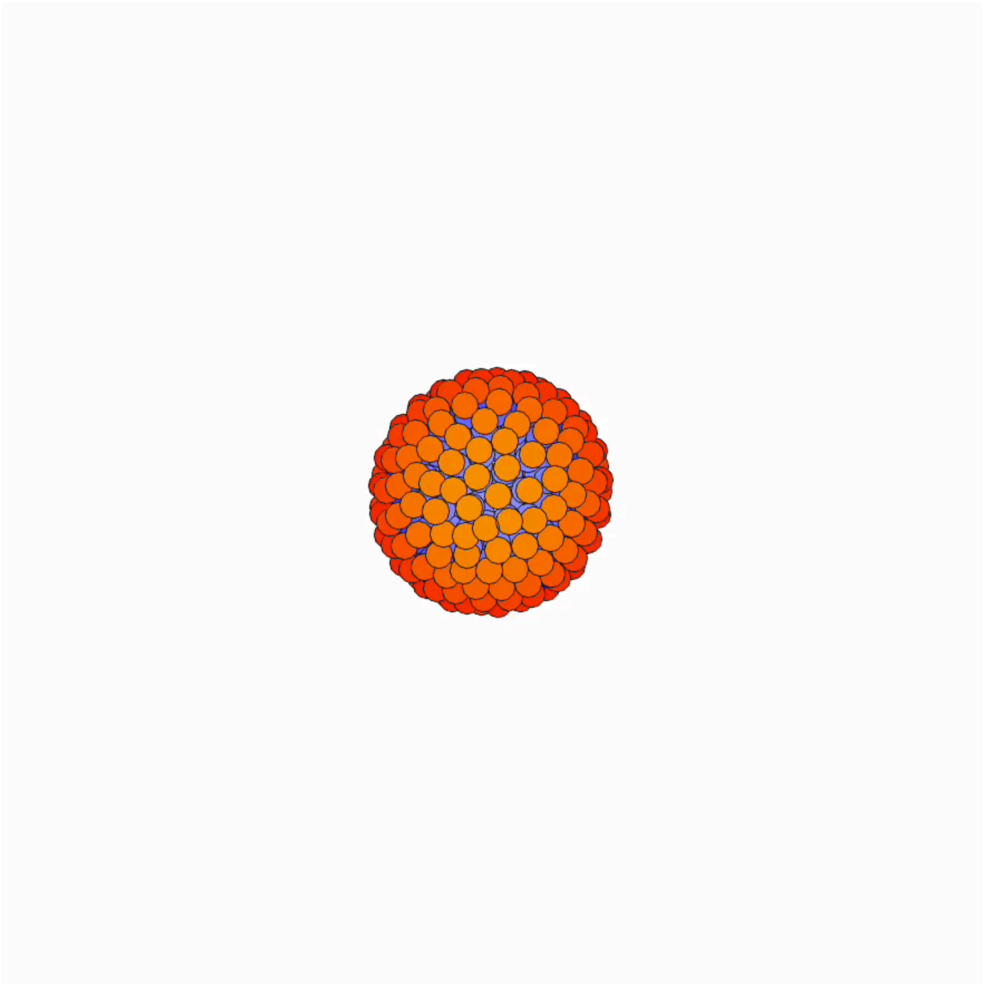


small are spherical
while large are folded

Greggio et al. (2013) *Development*

How do folded organoids form?





Boye et al. (2018) *bioRxiv*

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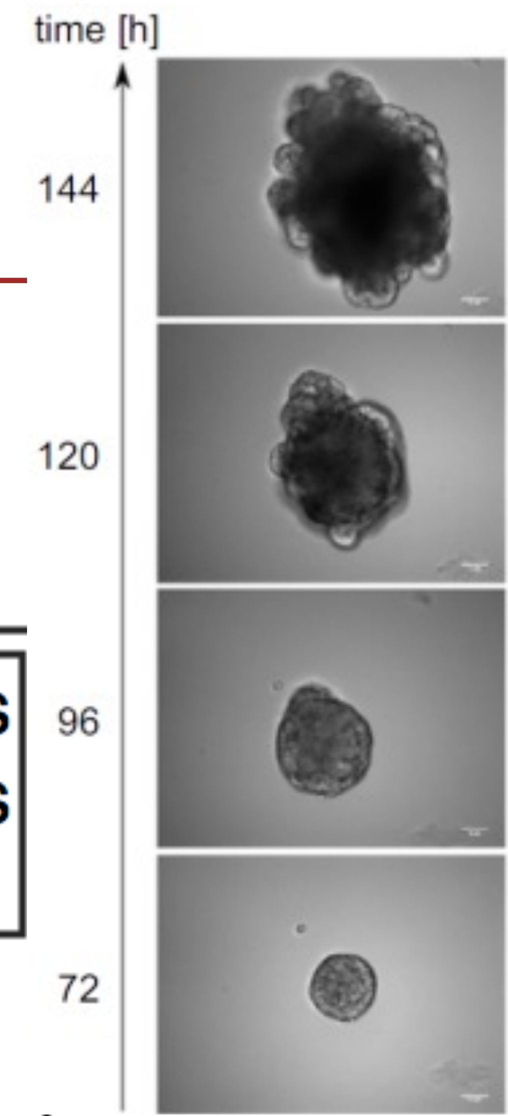
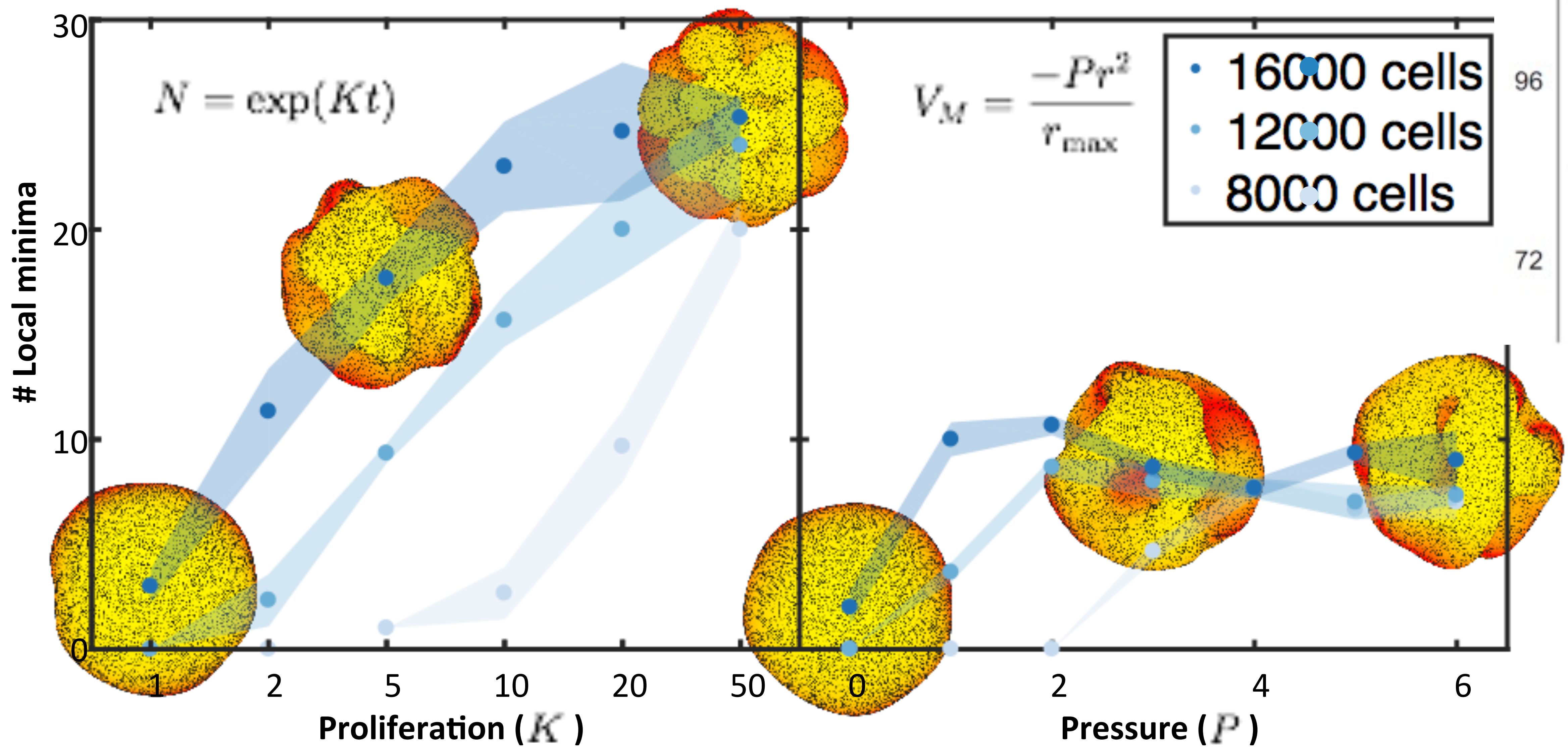
How do folded organoids form?

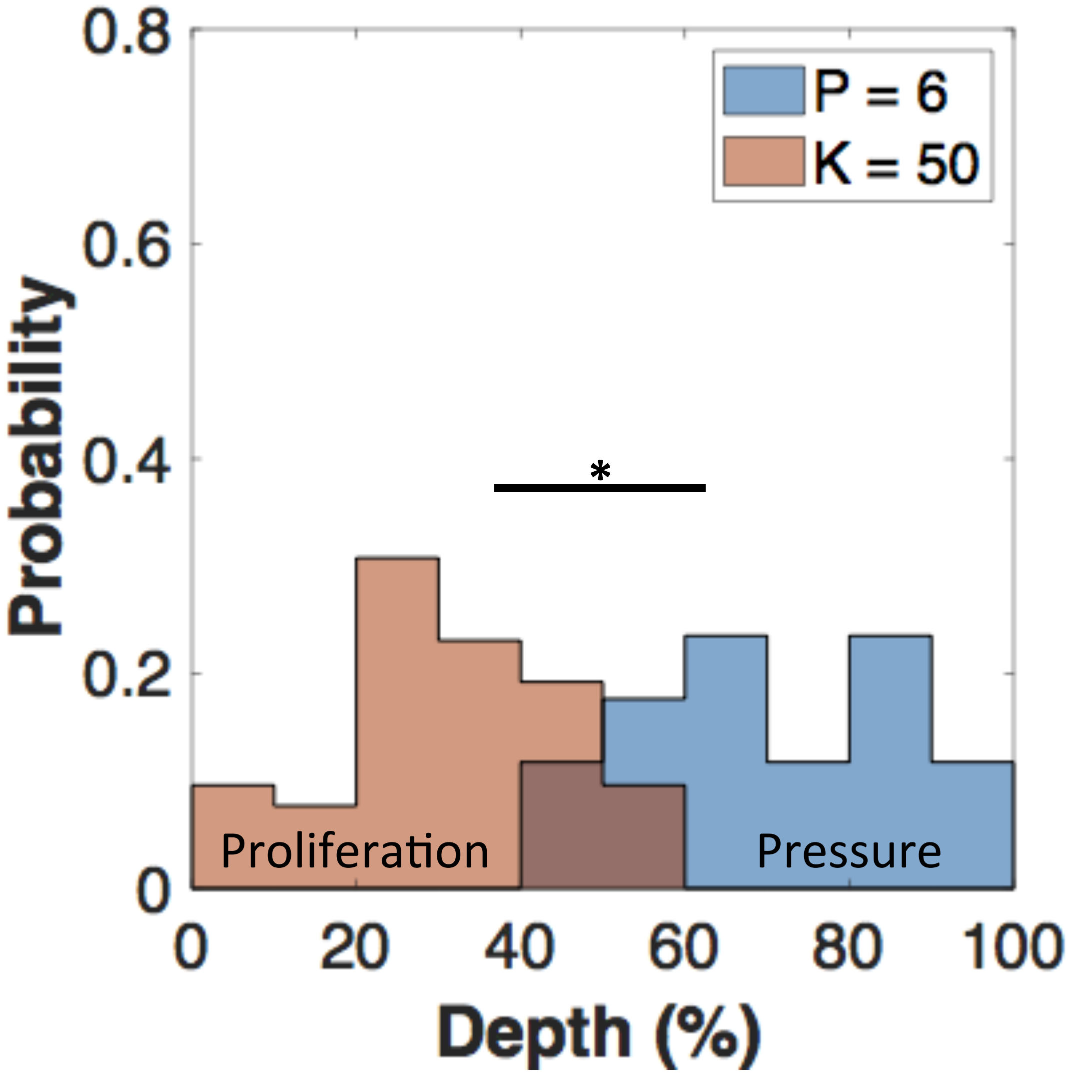


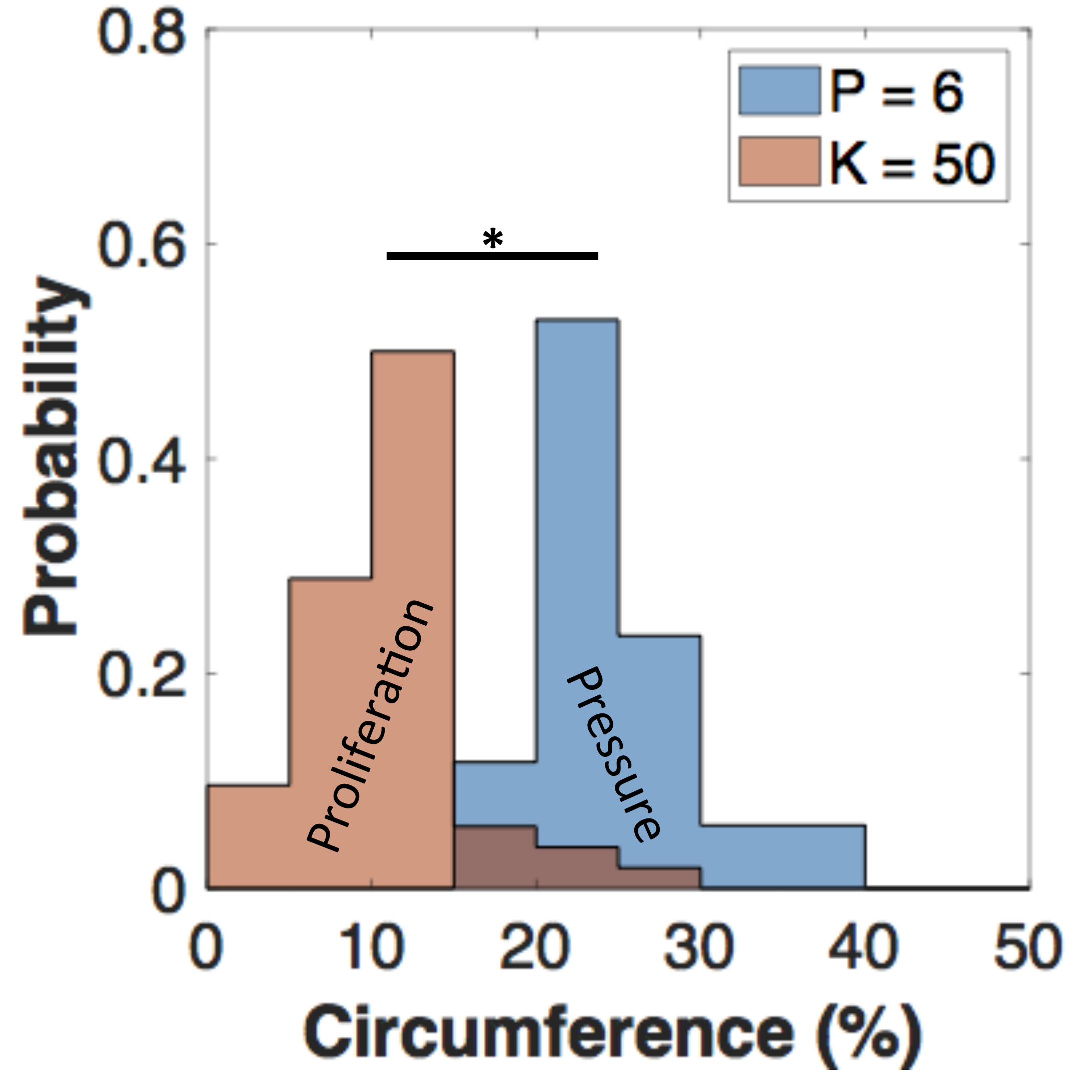
Svend Steffensen
Manuel F.-Larsen
& Anne Graphin-Botton
& Kim Sneppen (2016)



Boye et al. (2018) *bioRxiv*

Different depth and length of folds





Prediction: Pressure and proliferation make distinct folds

Boye et al. (2018) *bioRxiv*

Tubulogenesis

How do tubes with certain width and length form?

Adding a second polarity, the
Planar Cell Polarity

AB=skin in/outside
PCP=hair direction on your skin

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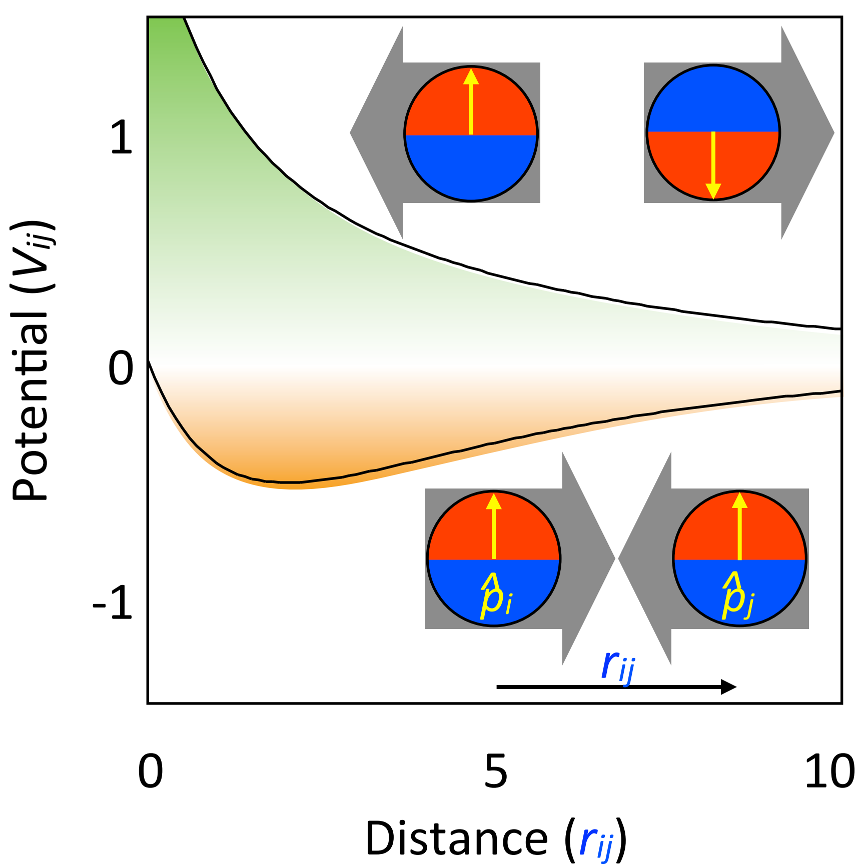
4) AB+PCP polarity:

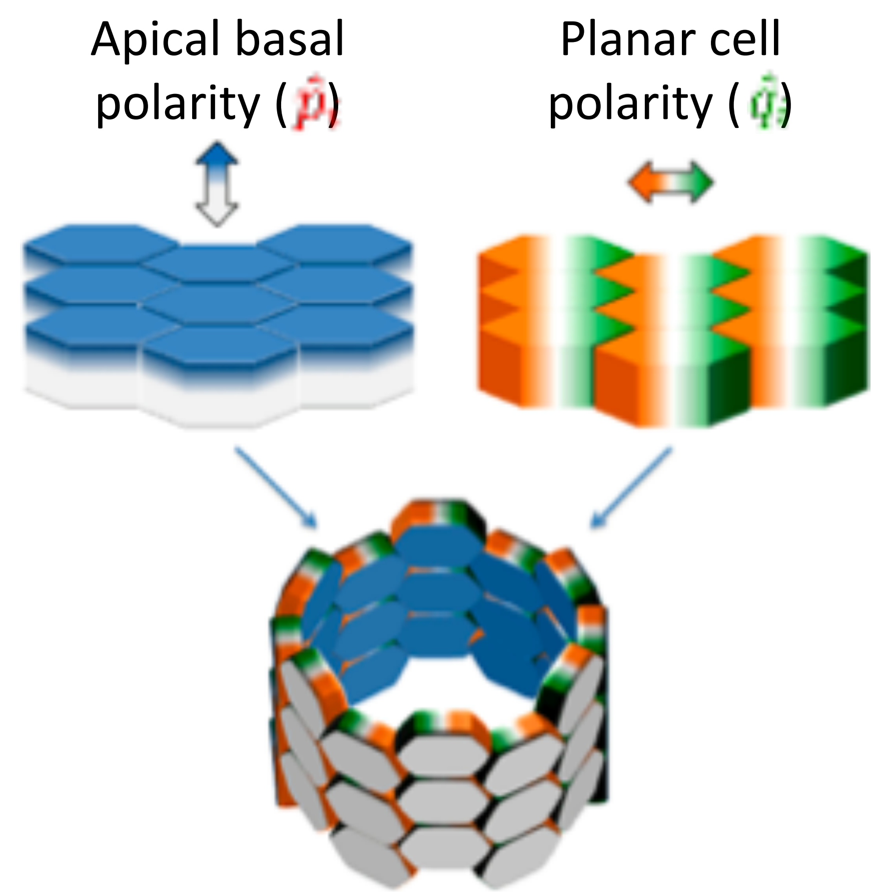
Potential between cells

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

Parameters

$$\lambda_1 + \lambda_2 + \lambda_3 = 1$$





Epithelial sheet

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

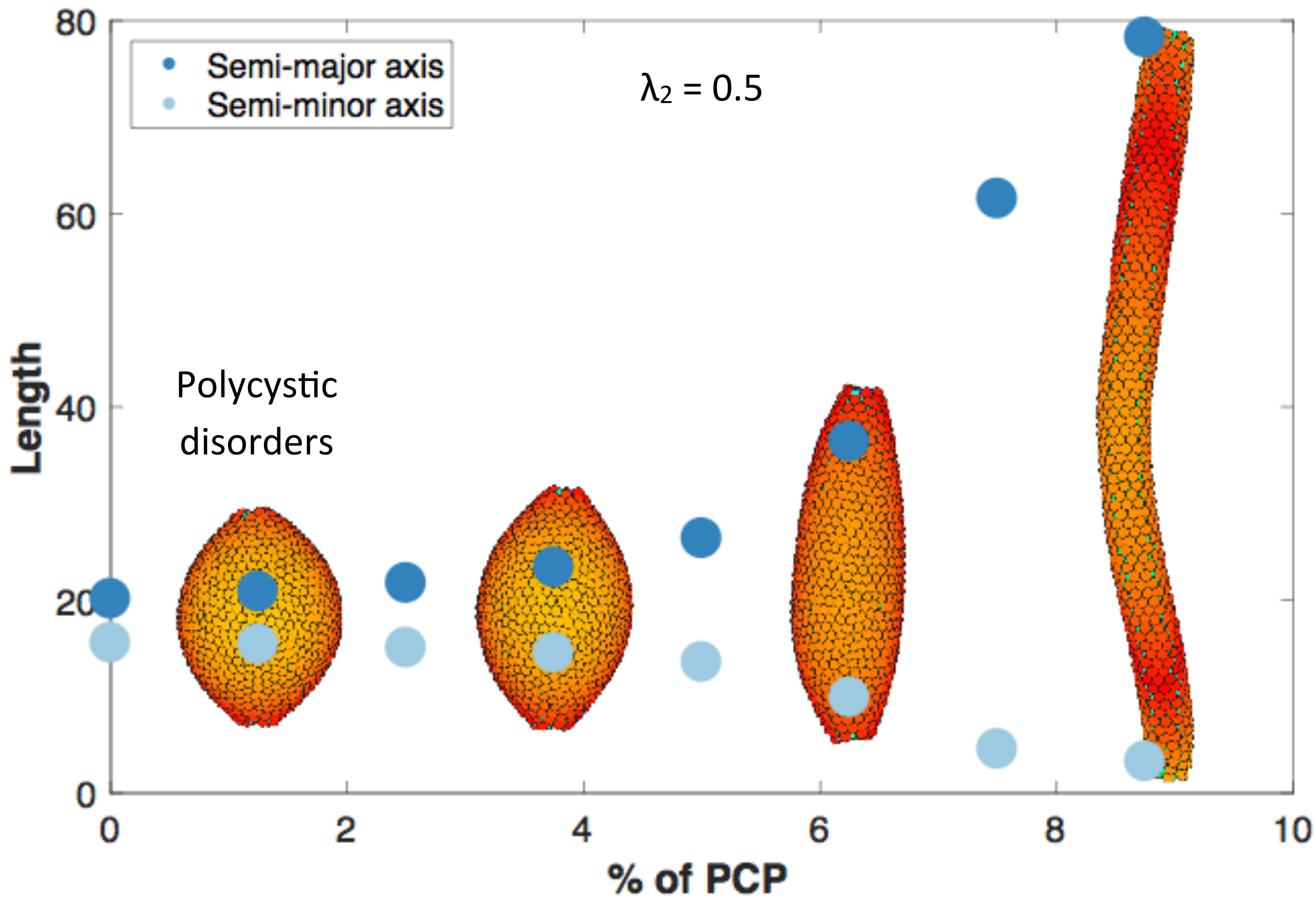
90° between polarities

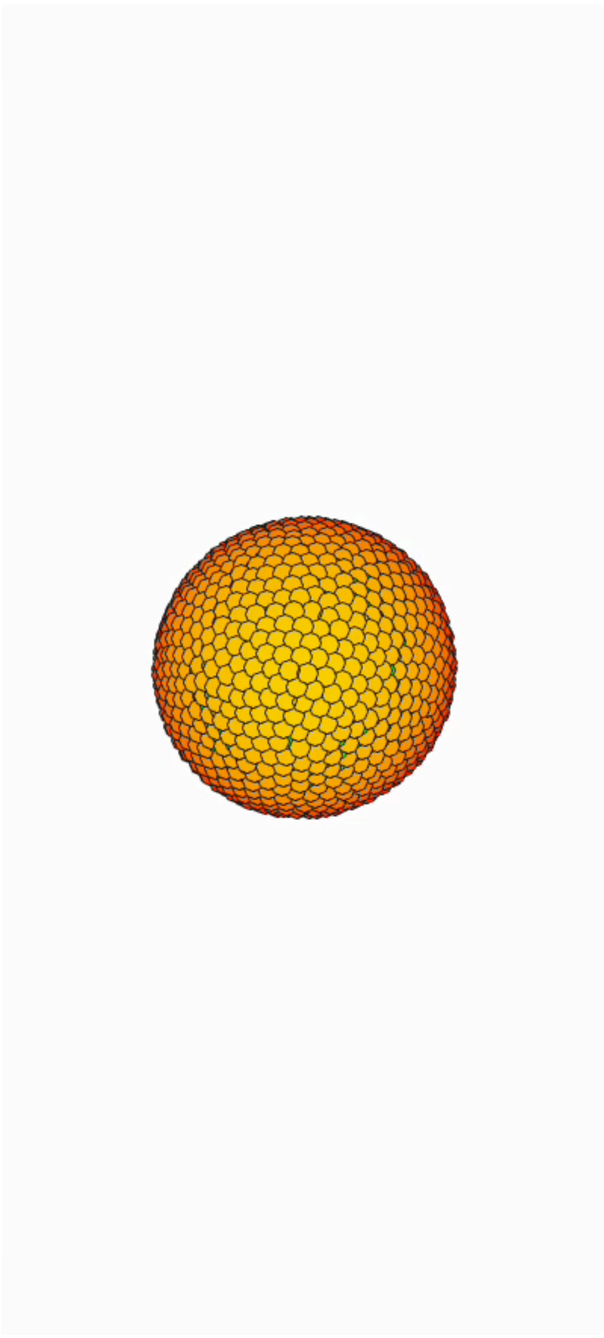
$$S_2 = (\hat{p}_i \times \hat{q}_i) \cdot (\hat{p}_j \times \hat{q}_j)$$

Convergent extension

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

4a) How do tubes form:

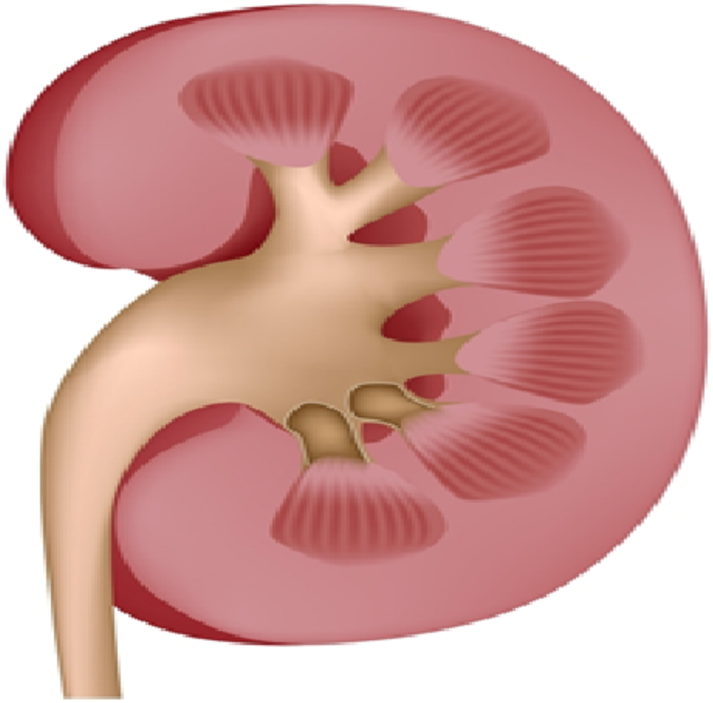




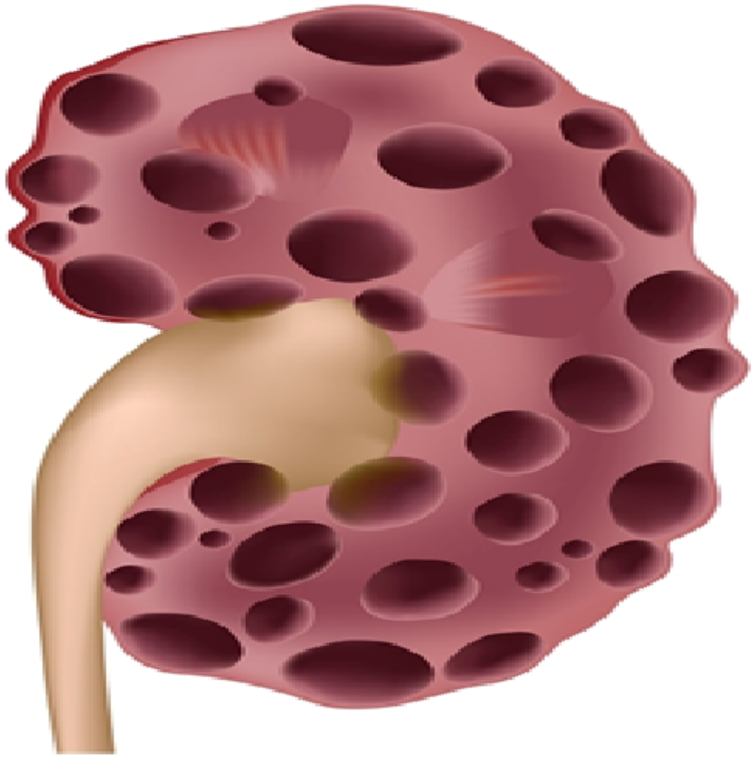
Prediction: Strength of AB vs. PCP controls length and width

Polycystic Kidney Disease

Normal kidney



Diseased kidney



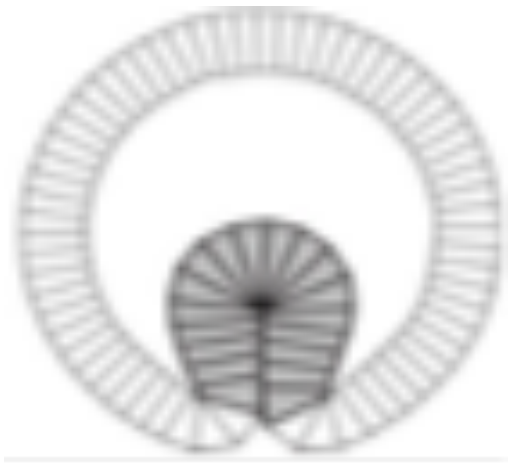
Absence of PCP,
less tubes,
Instead spherical holes

Invagination

What drives invagination across species?

Vertex models

Gastrulation

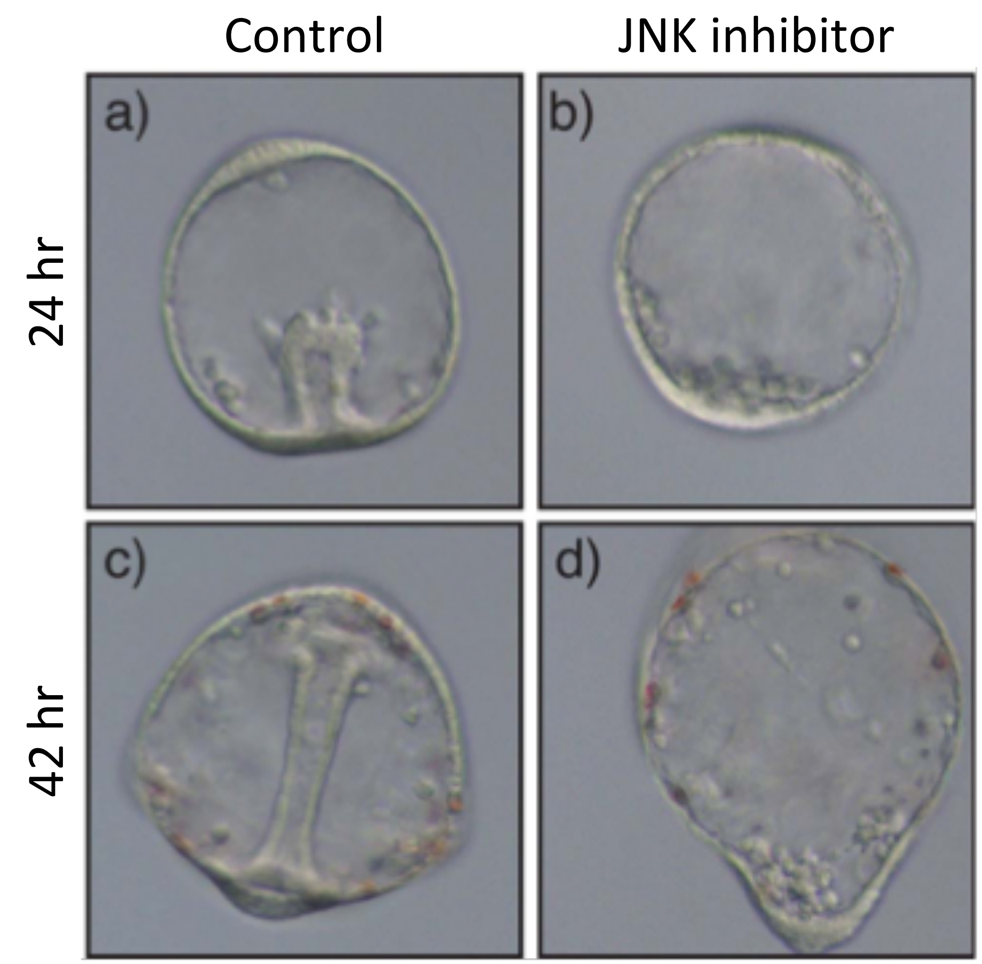


Brezavscek et al. (2012)

Neural tube formation

Alt et al. (2017)

What drives invagination?

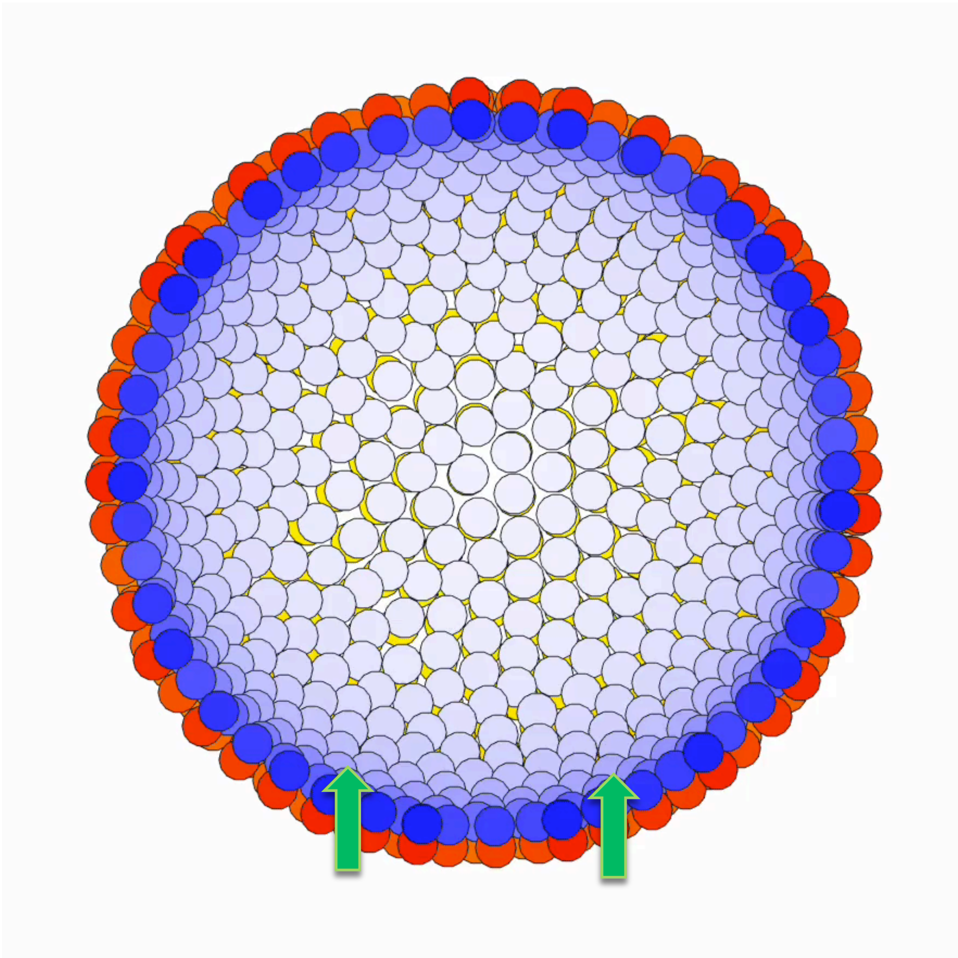


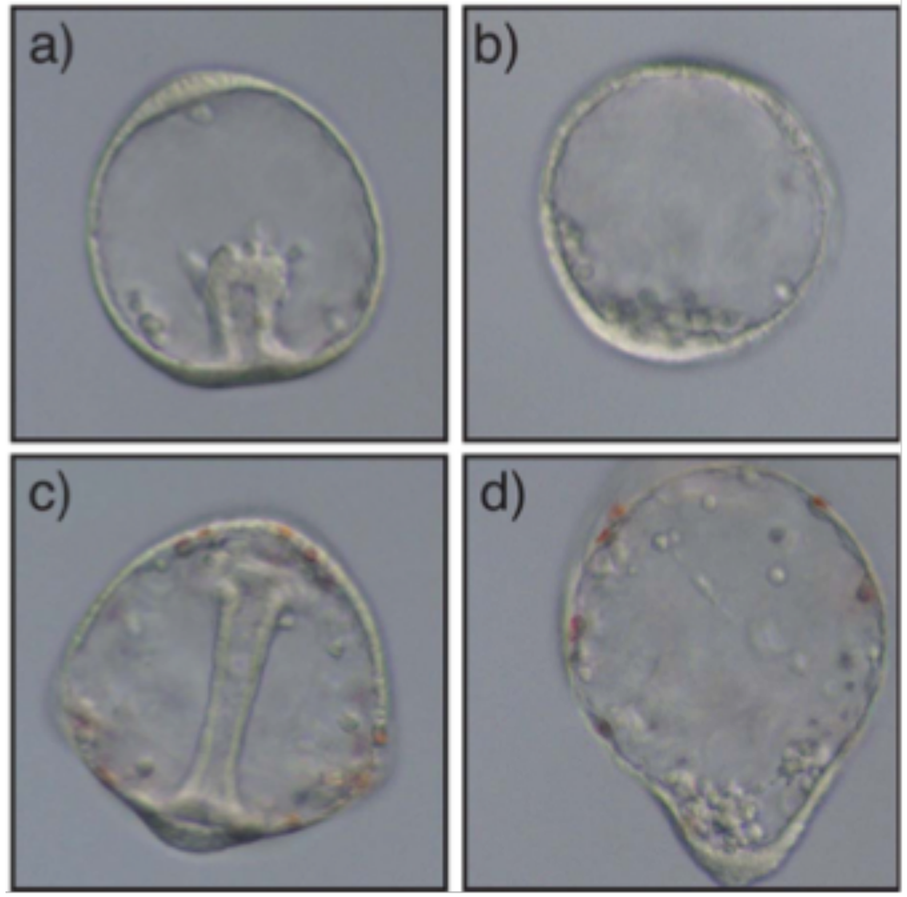
Long et al. (2015)

Boye et al. (2018) *bioRxiv*

What drives invagination?

Gastrulation



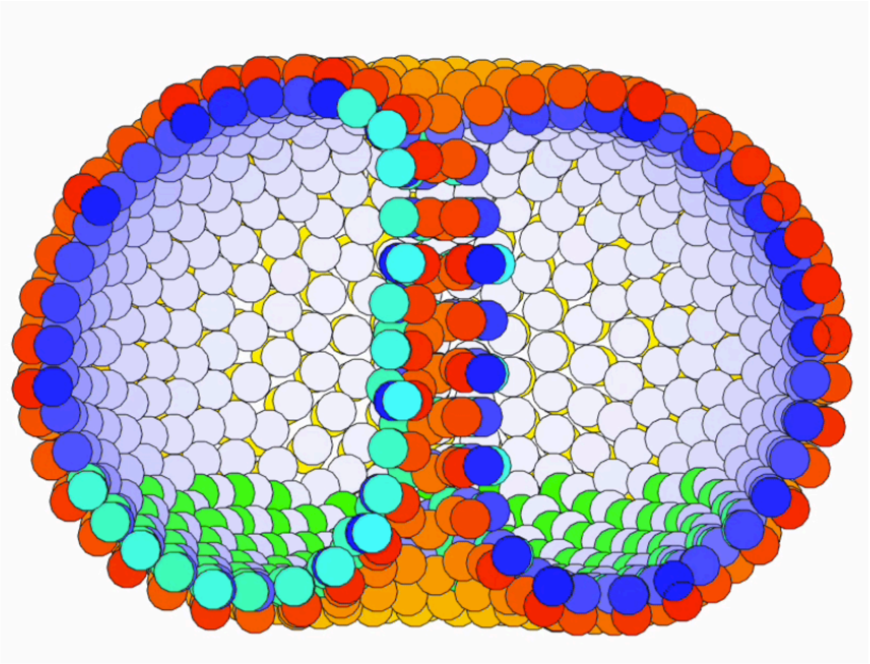


Long et al. (2015)

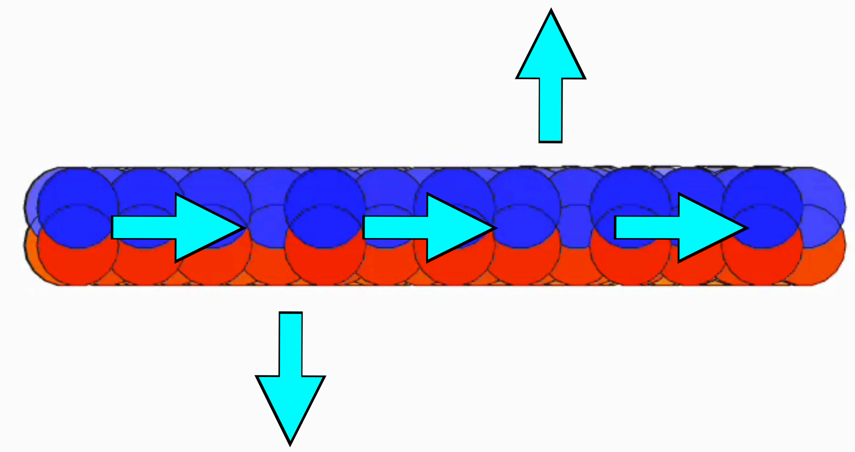
Boye et al. (2018) *bioRxiv*

What drives invagination?

Gastrulation



Neurulation



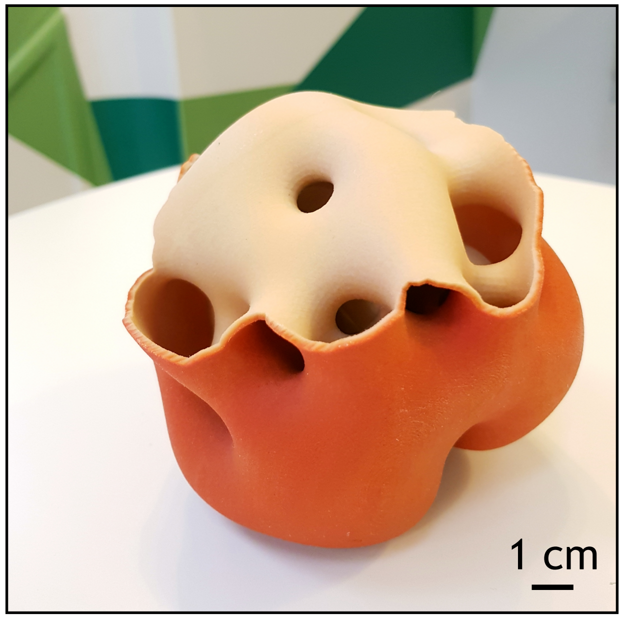
Prediction: Different initial conditions give different types of invagination

Conclusion

Take home messages

Conclusion

1. Tool to model impact of cell polarities
2. Complex diverse stable shapes
3. Distinct organoid fold morphology
4. Tube length and width given by PCP
5. PCP drives gastrulation and neurulation



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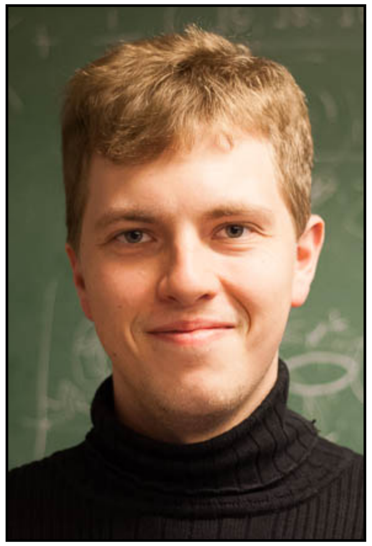
Collaborators:

Silas Boye Nissen
NBI

Ala Trusina
NBI

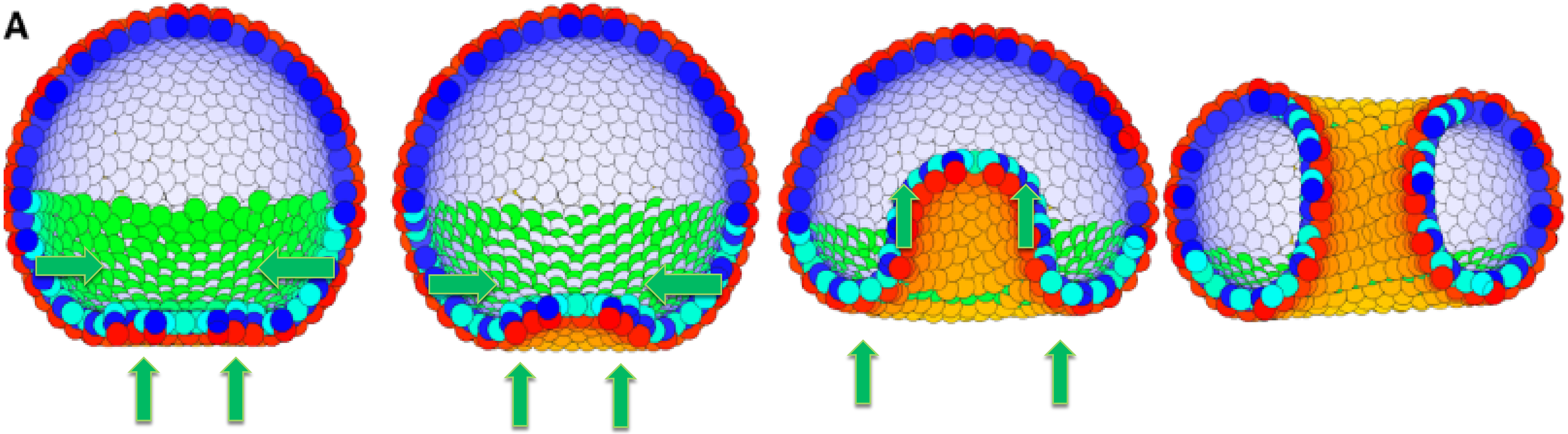


Steven Rønhild
NBI

Sophie M. Morgani
DanStem

Joshua M. Brickman
DanStem

(Sea-Urchin) Gastrulation



PCP is sufficient for neural plate bending and neural tube closure

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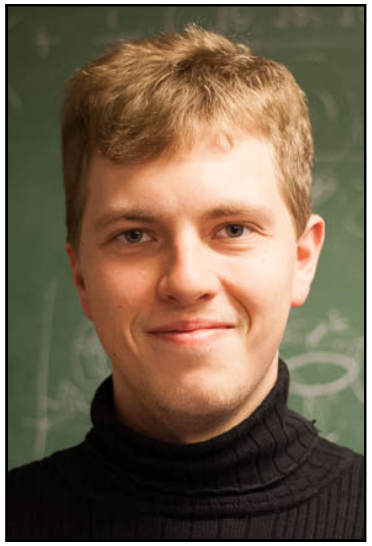
Coauthors

Mogens H. Jensen
Niels Bohr Inst.

Silas Boye Nissen
NBI

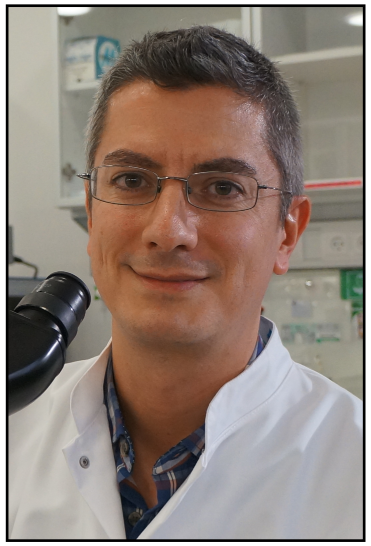


Steven Rønhild
Niels Bohr Inst.

Ala Trusina
Niels Bohr Inst.

Marta Perera
DanStem

Sophie M. Morgani
DanStem



Javier M. Gonzalez
DanStem

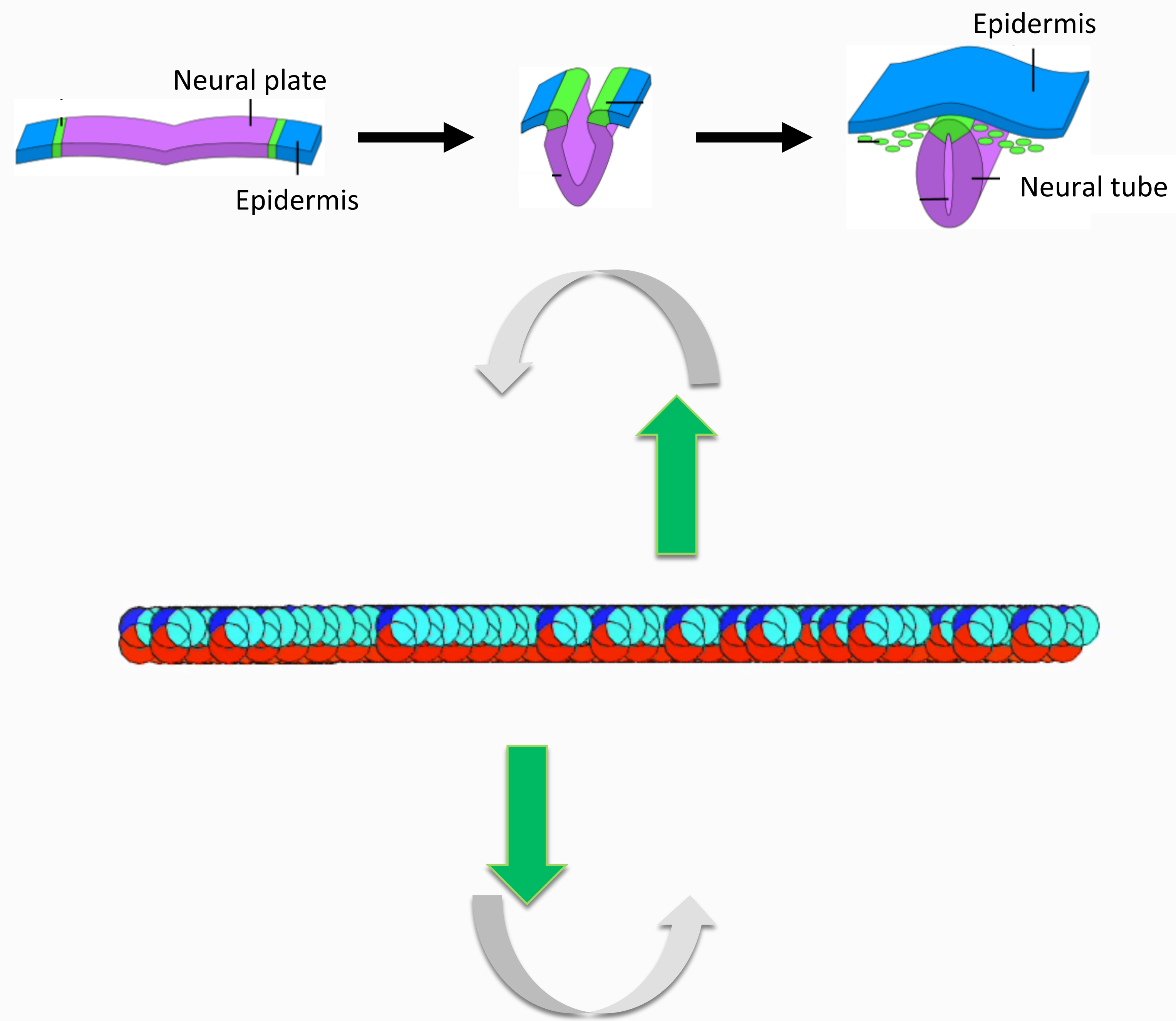
Joshua M. Brickman
DanStem

Danmarks Grundforskningsfond
Danish National Research Foundation

DanStem

novo nordisk

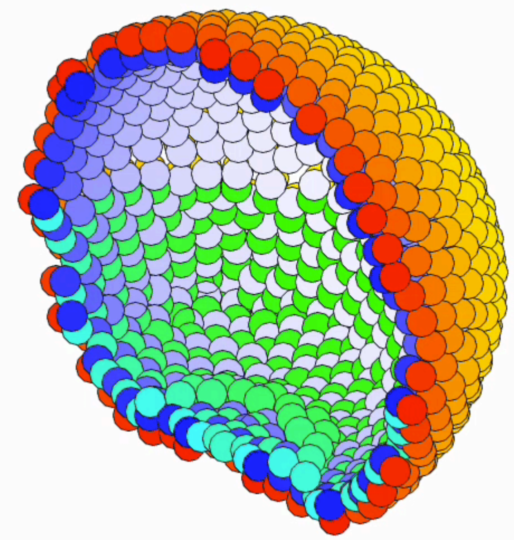
4b) Neural tube formation



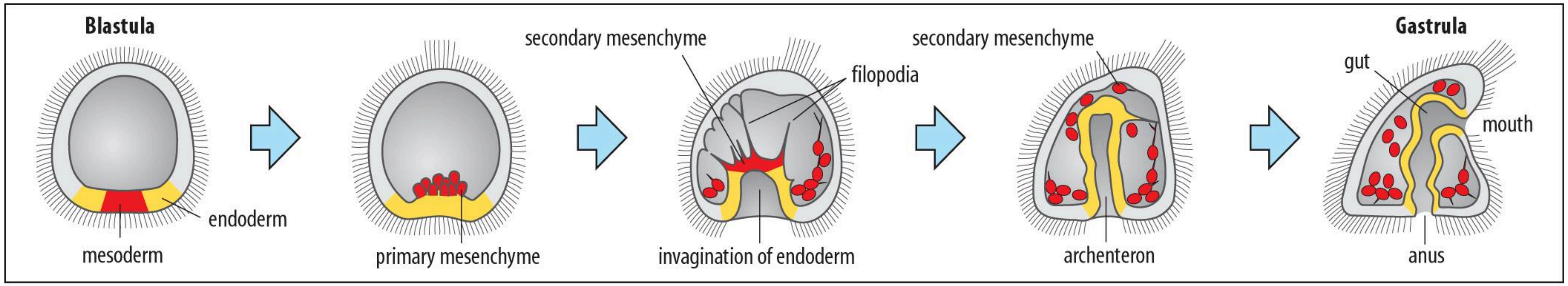
PCP is sufficient for neural plate bending and neural tube closure

Use local fixed PCP to twist plane locally

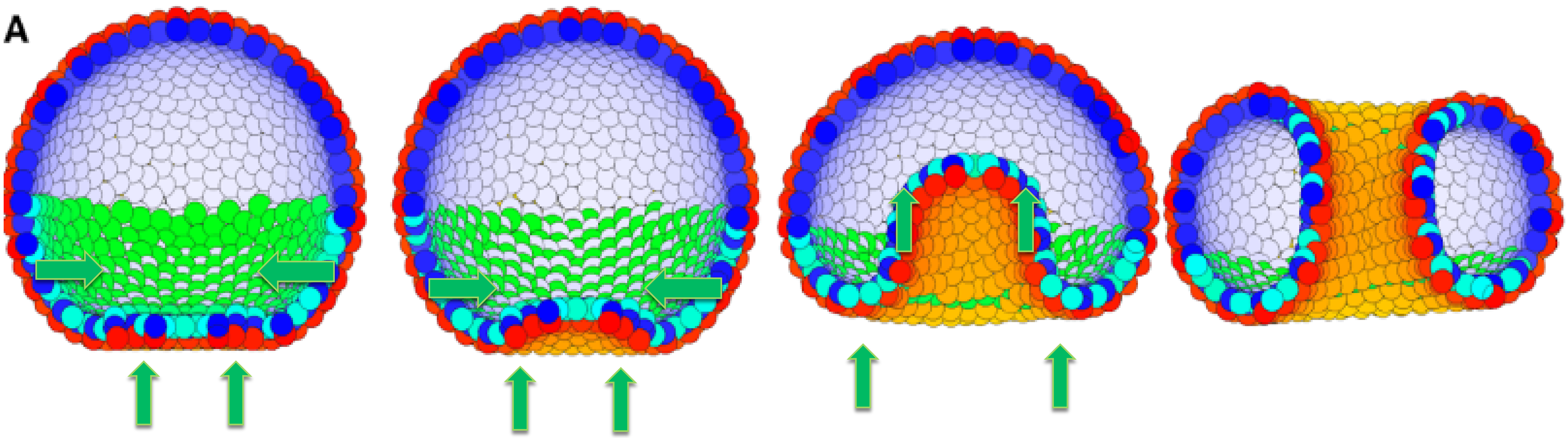
4c) Gastrulation in Sea Urchin



PCP is sufficient to initiate invagination and drive elongation



(Sea-Urchin) Gastrulation



PCP is sufficient for neural plate bending and neural tube closure

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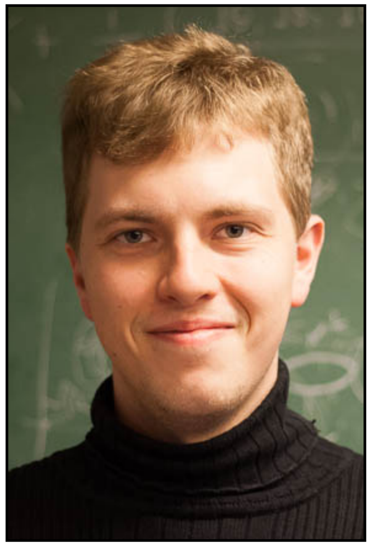
Acknowledgments

Silas Boye Nissen
NBI

Ala Trusina
NBI

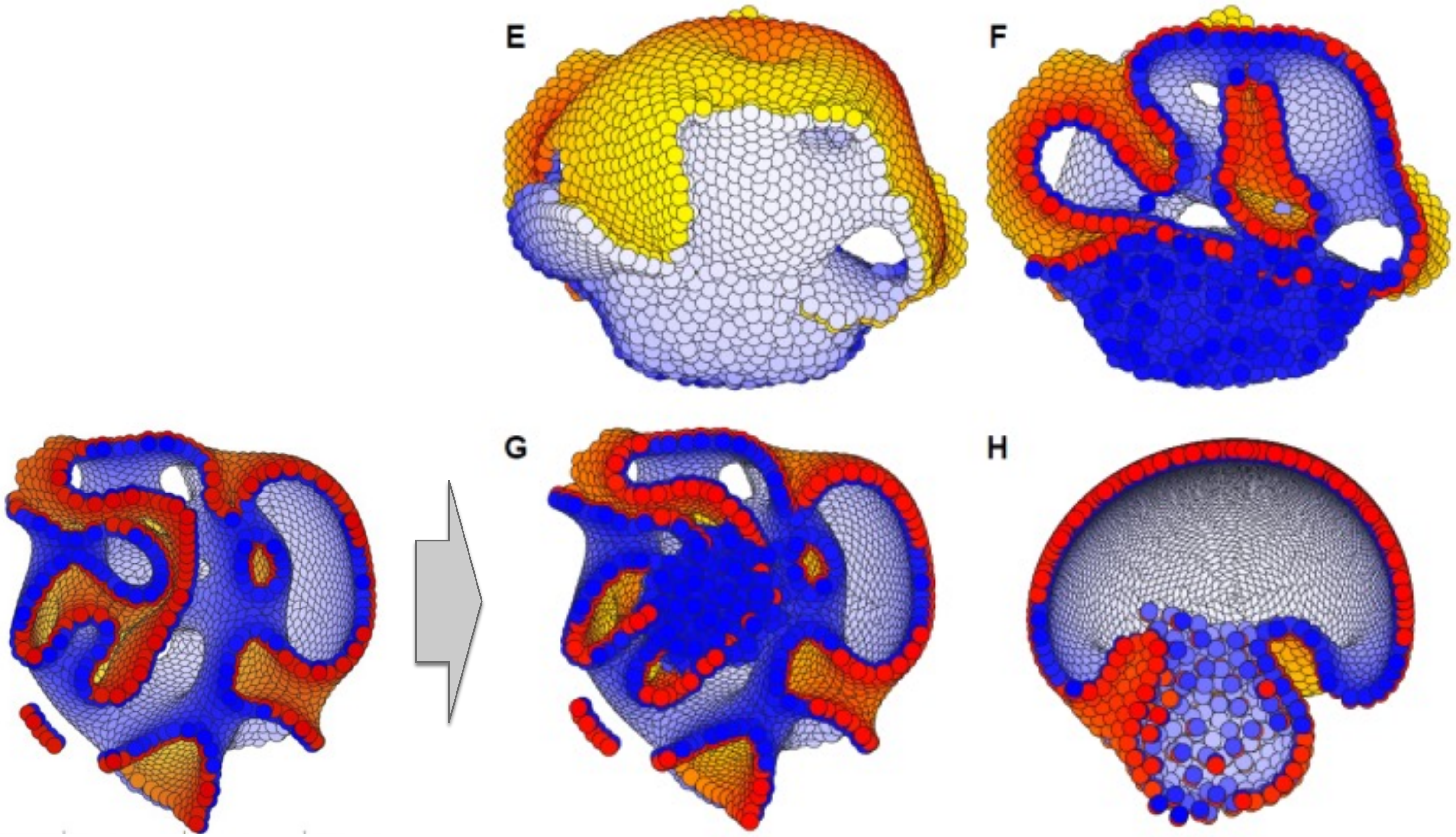


Steven Rønhild
NBI

Sophie M. Morgani
DanStem

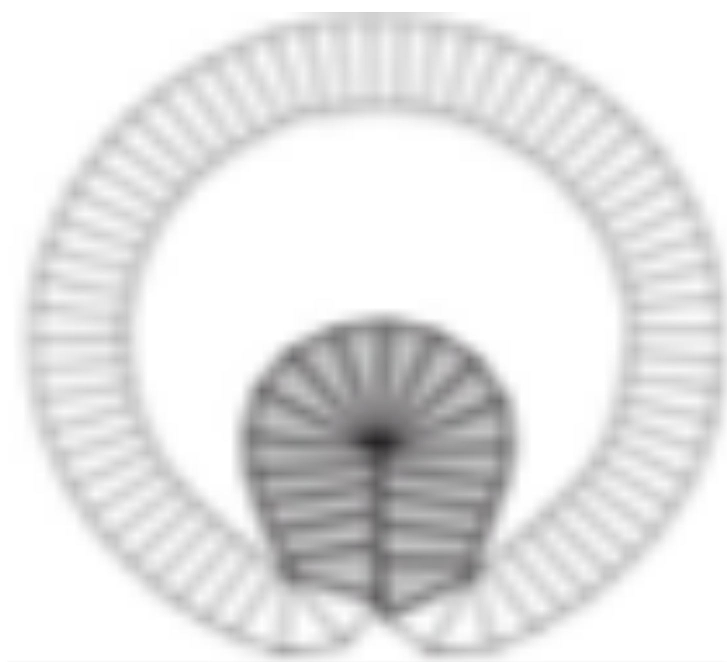
Joshua M. Brickman
DanStem

5) Note: Tumor = loss of polarity



Vertex models

Gastrulation



Brezavscek et al. (2012),
buckling from favoring free cell surface against interacting cells. (2d model, each cell a deformed square)

Neural tube formation

Alt et al. (2017), Monier et al. (2015)
vertex models: assign a value to polygon cell edges representing the density of planar polarity proteins. Monier use apoptosis to drive above formation

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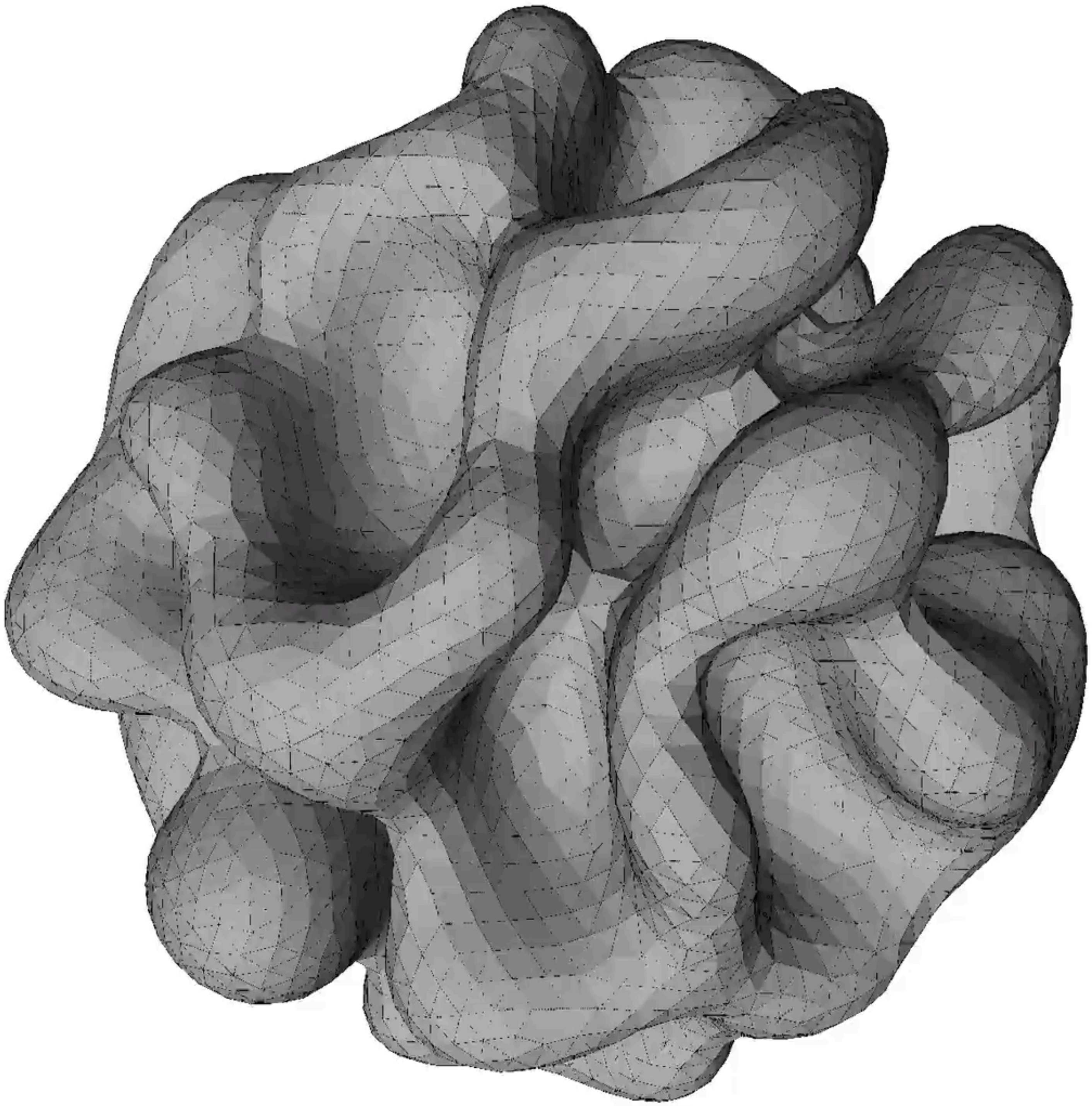
Next step…:

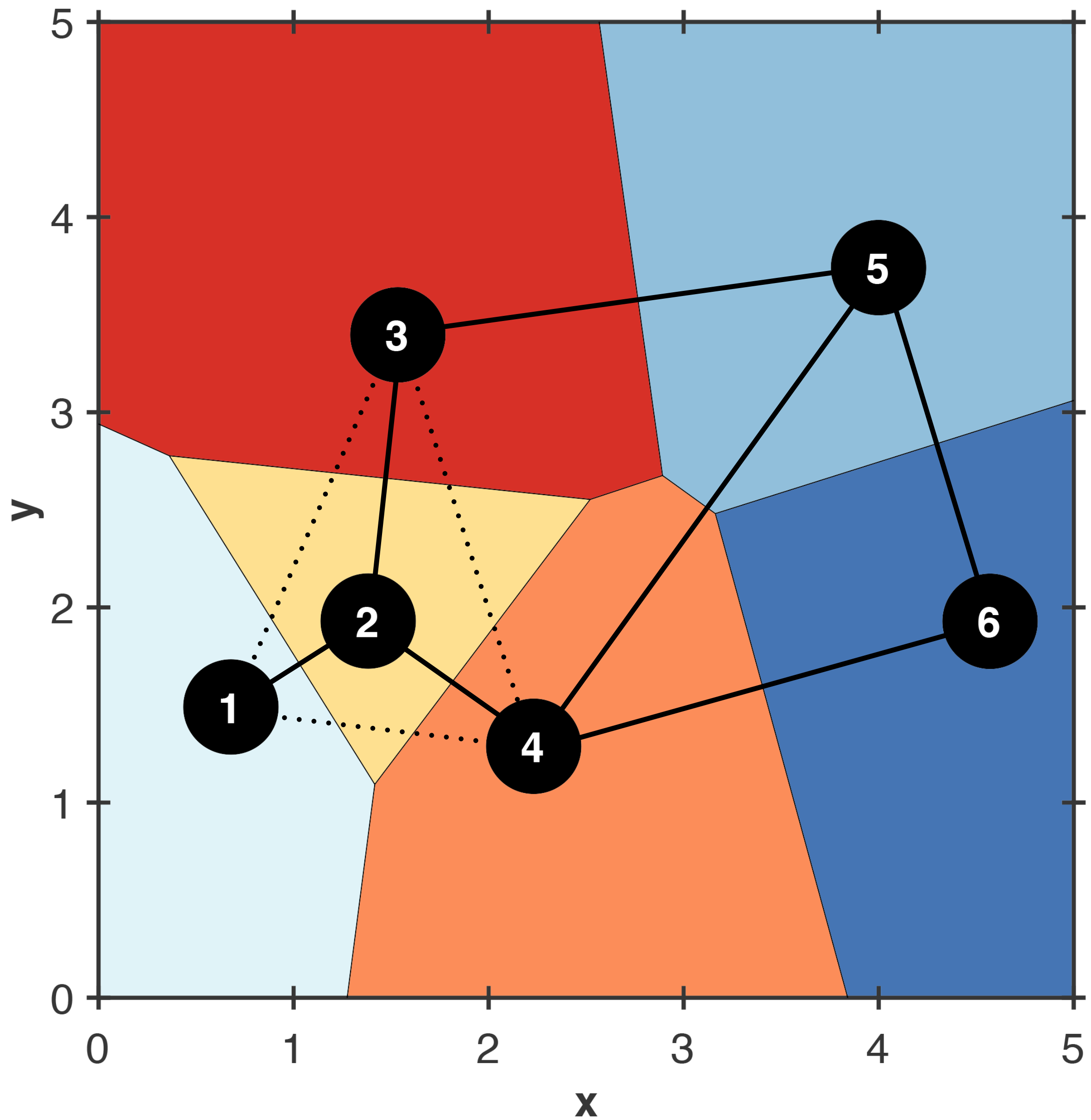
Online STL viewer



https://www.viewstl.com/

Interacting neighbors

Who interact?



Solid lines do, dashed do not

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

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

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

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