Polarity controlled patterning in mammary bilayers

Chaste workshop 2023

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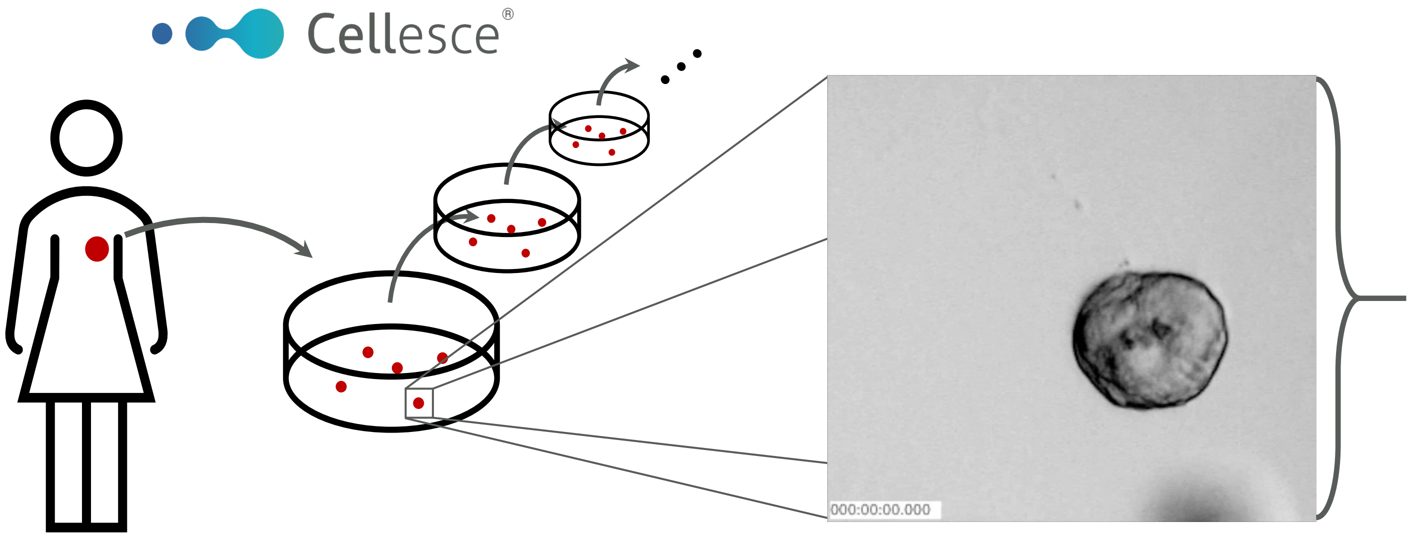
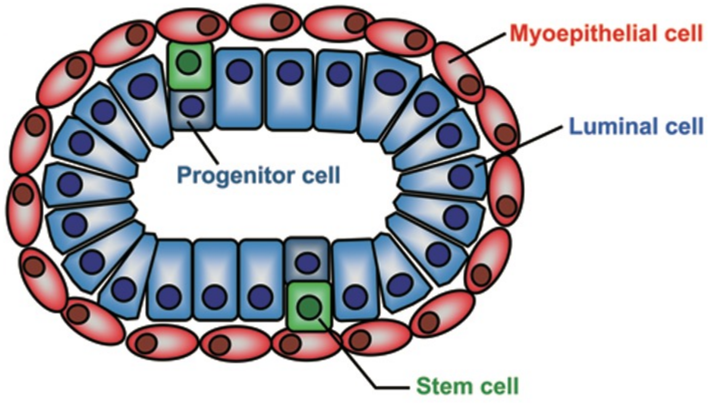
wcmb

Plasticity in mammary organoids



Bilayer structure



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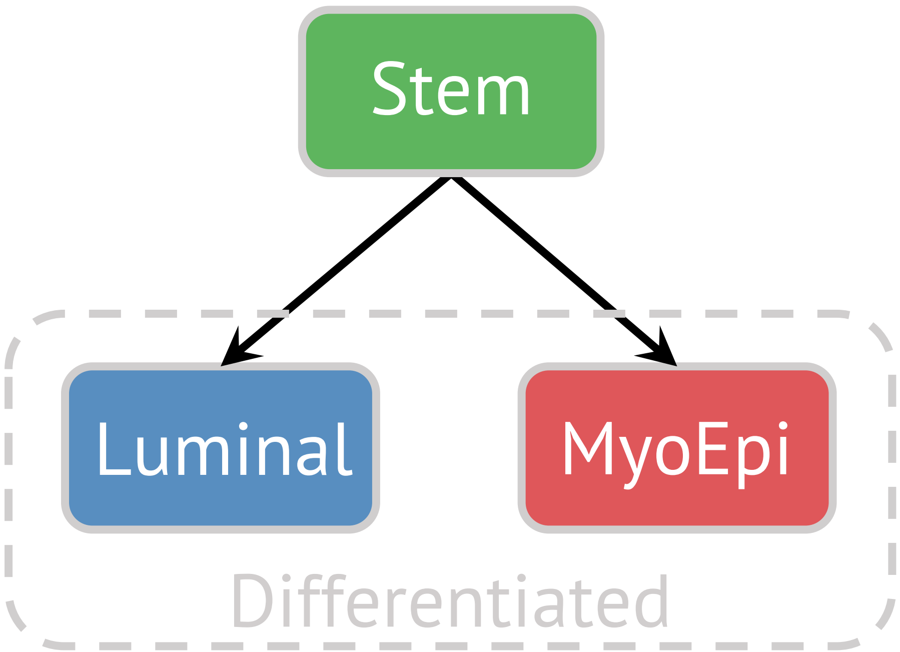
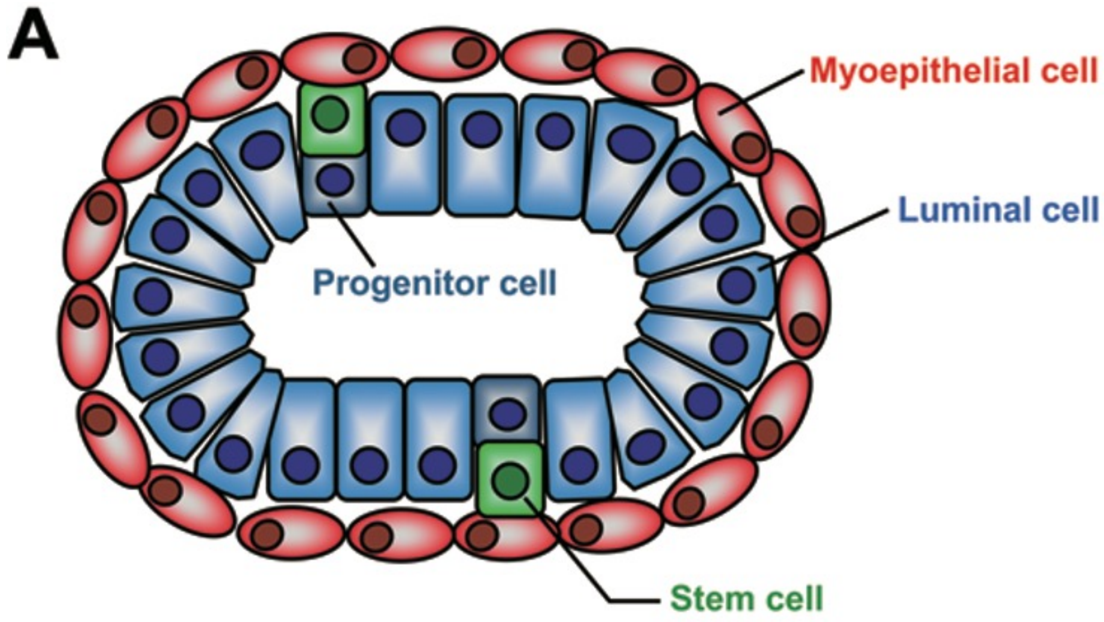
Plasticity in mammary organoids

Traditional hierarchy
in mammary tissue



Observed hierarchy
in mammary organoids



Organoid regeneration induces changes in cell identity

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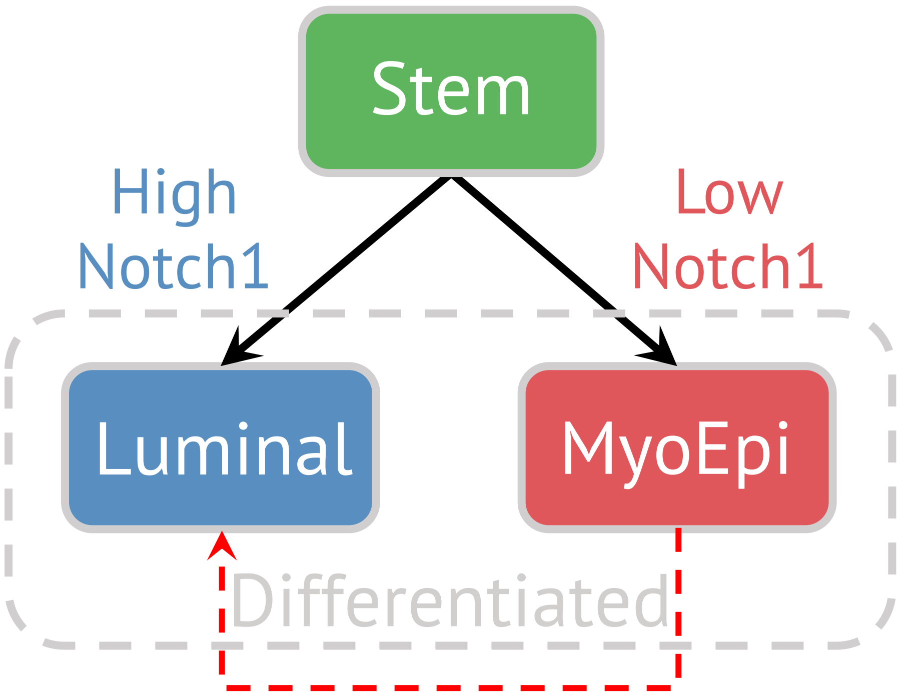
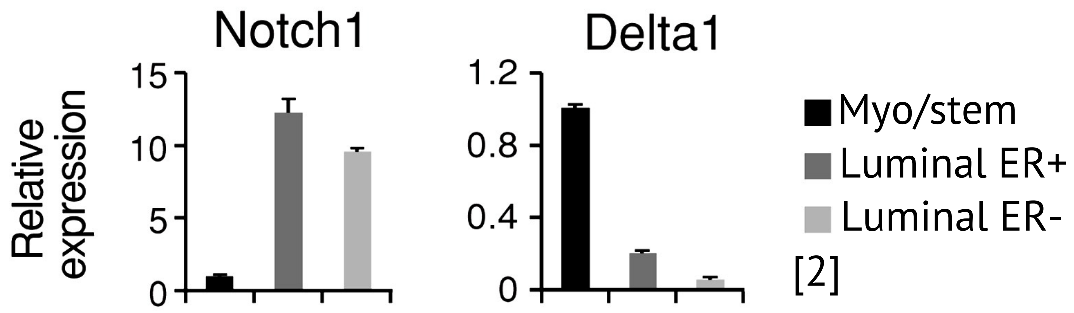
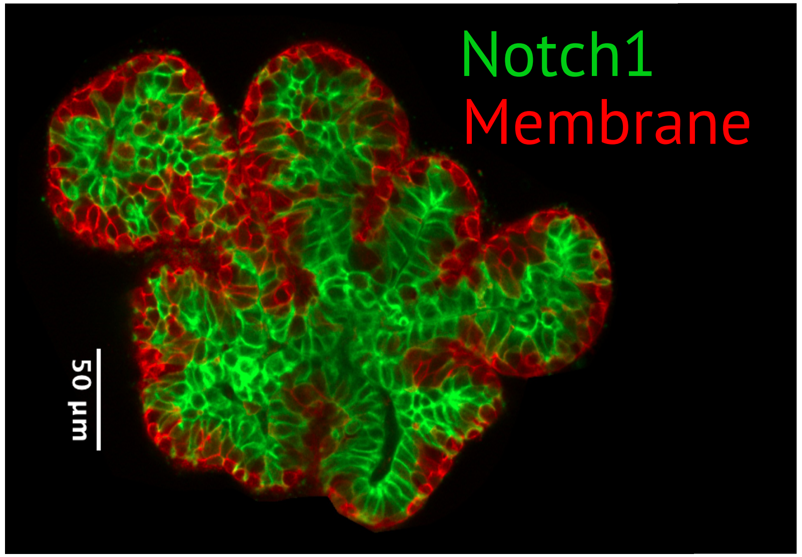
Mechanisms of cell-fate determination

Notch1-dependent cell-fate decisions



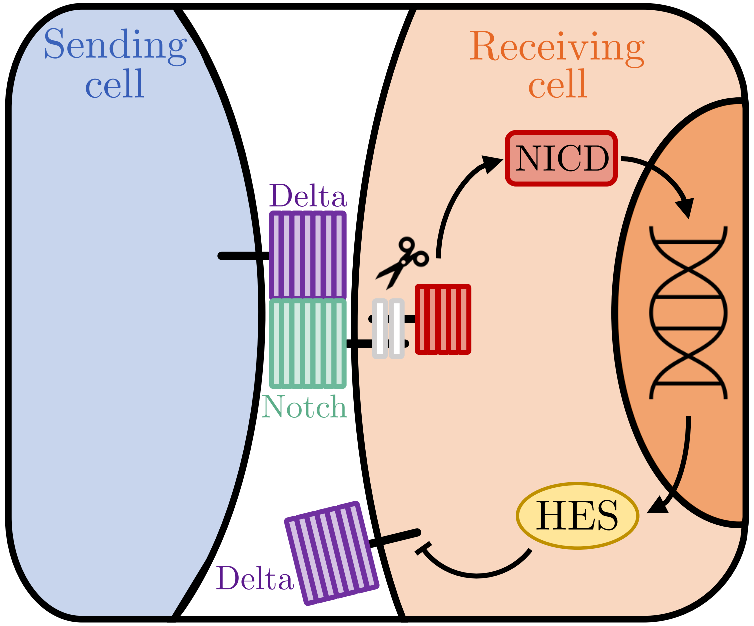
Experimental Notch1 expression





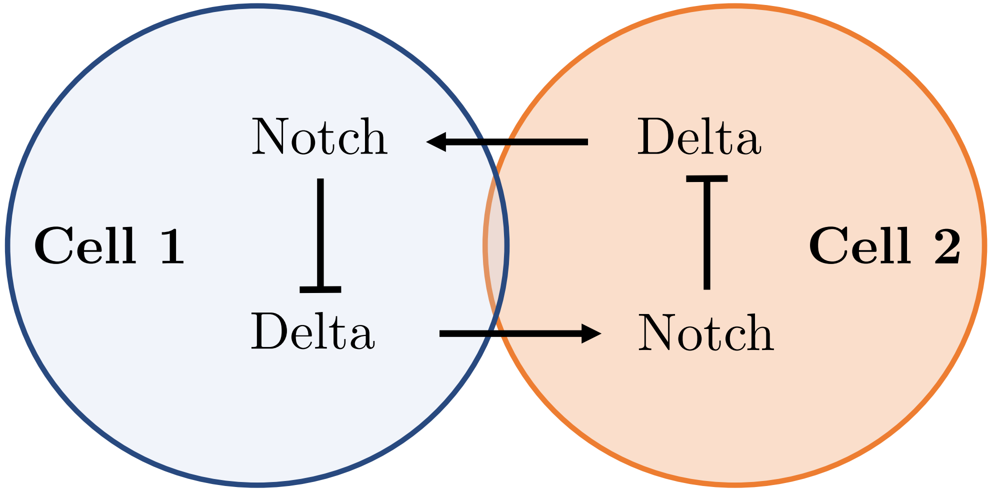
Laminar patterns of Notch1 expression

Notch patterning

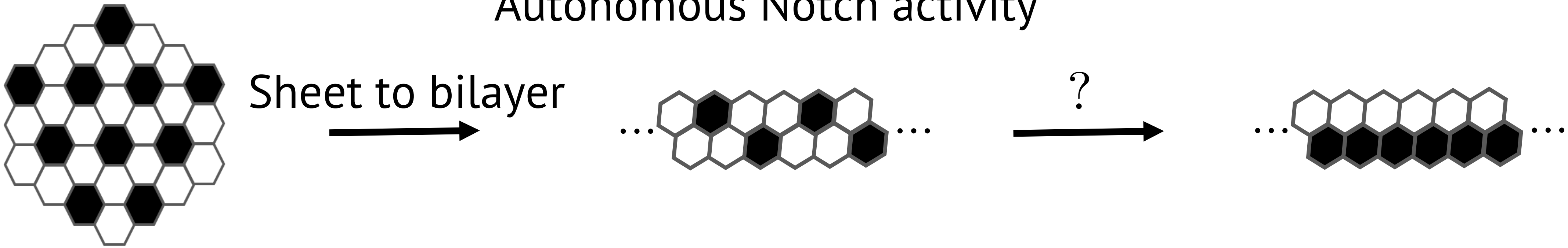


A simple model of Notch signalling

Collier *et al.* (1996)



Autonomous Notch activity



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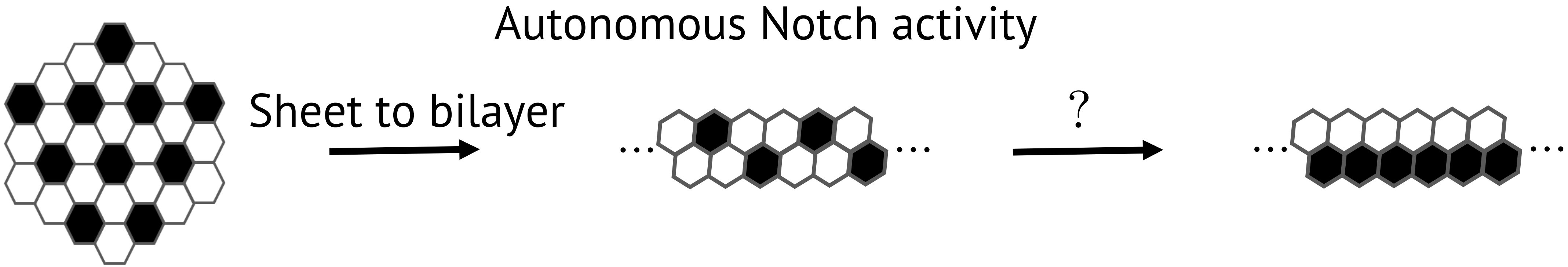
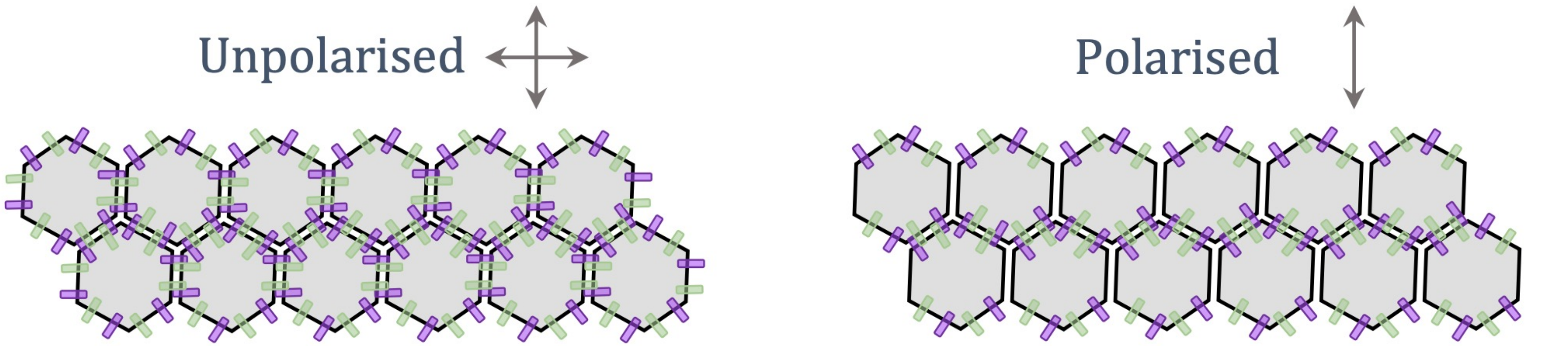
Notch patterning



Possible mechanisms to promote laminar patterning:

1

Cell signalling polarity



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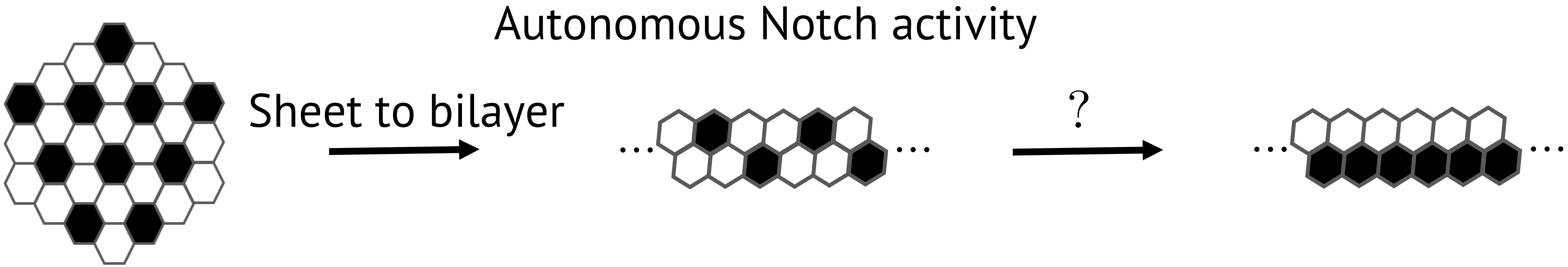
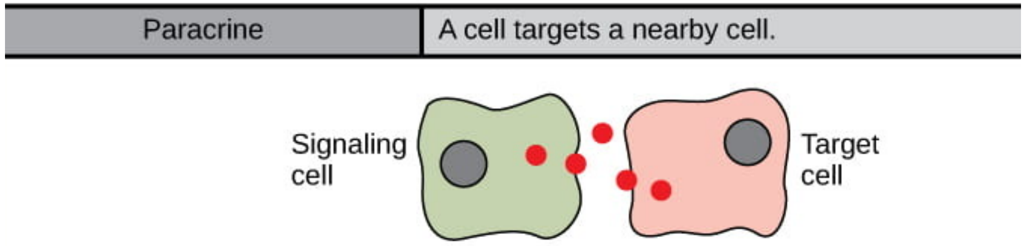
Notch patterning

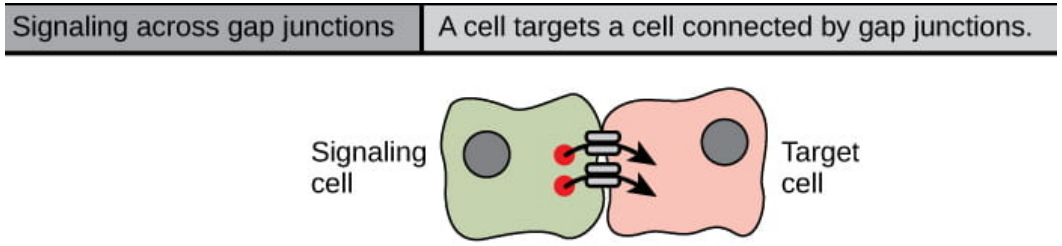


Possible mechanisms to promote laminar patterning:

2

Multiple signals (crosstalk)





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Notch patterning

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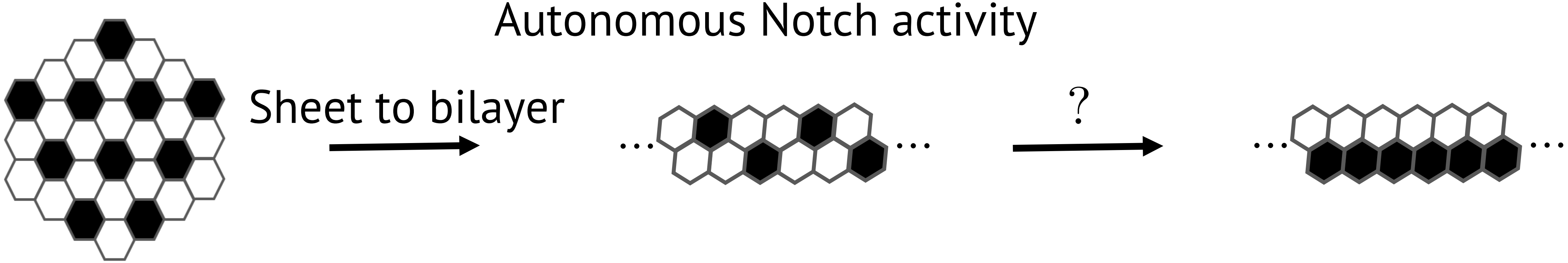

Possible mechanisms to promote laminar patterning:

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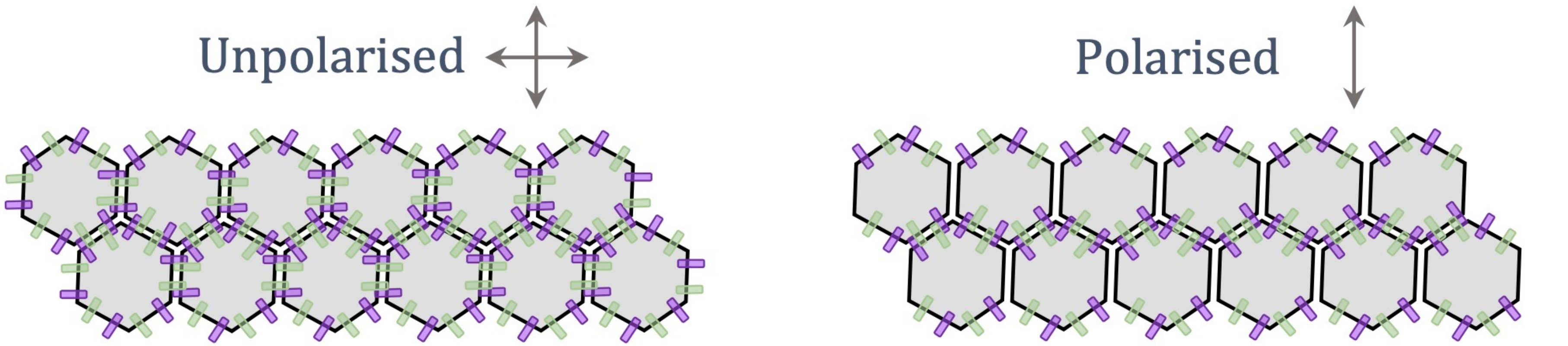

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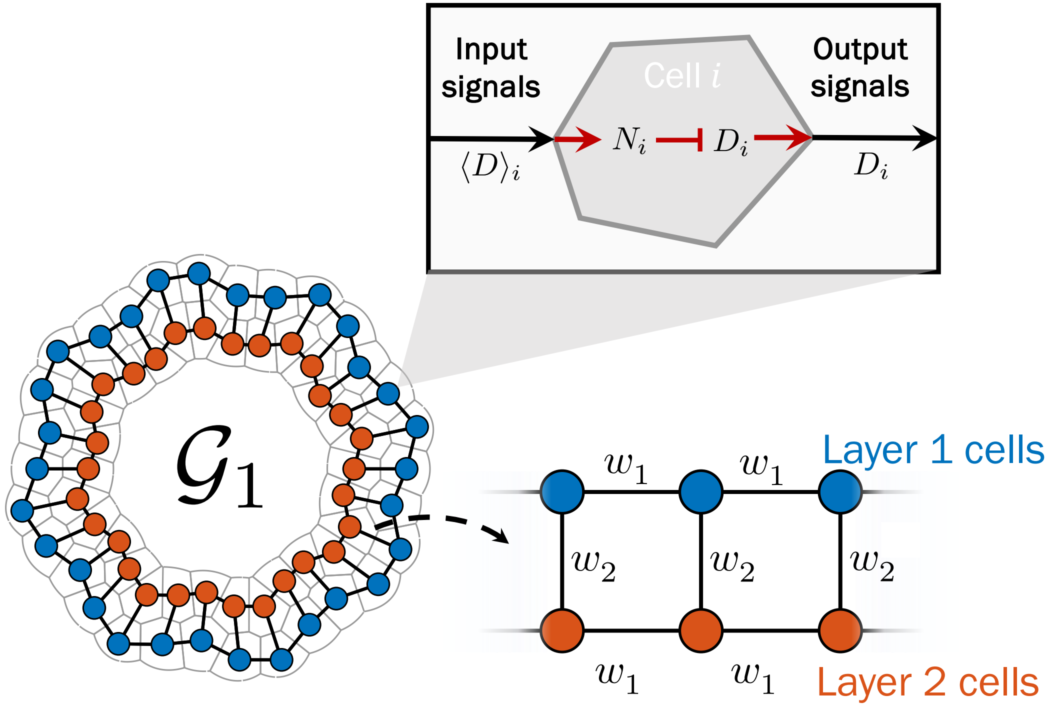
Combing tools for discrete pattern analysis

Network coupled ODEs (IO systems)

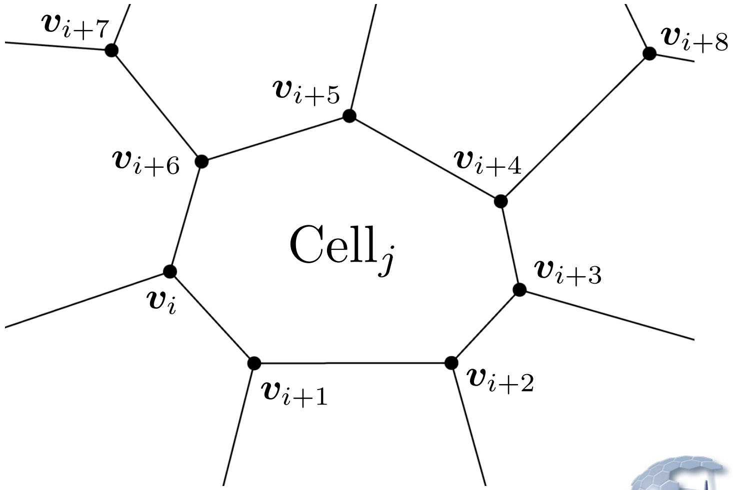


Spatially static

❶ Calibrating polarity control

❷ Calibrating network regimes

Cell-based modelling



Spatially dynamic

Chaste

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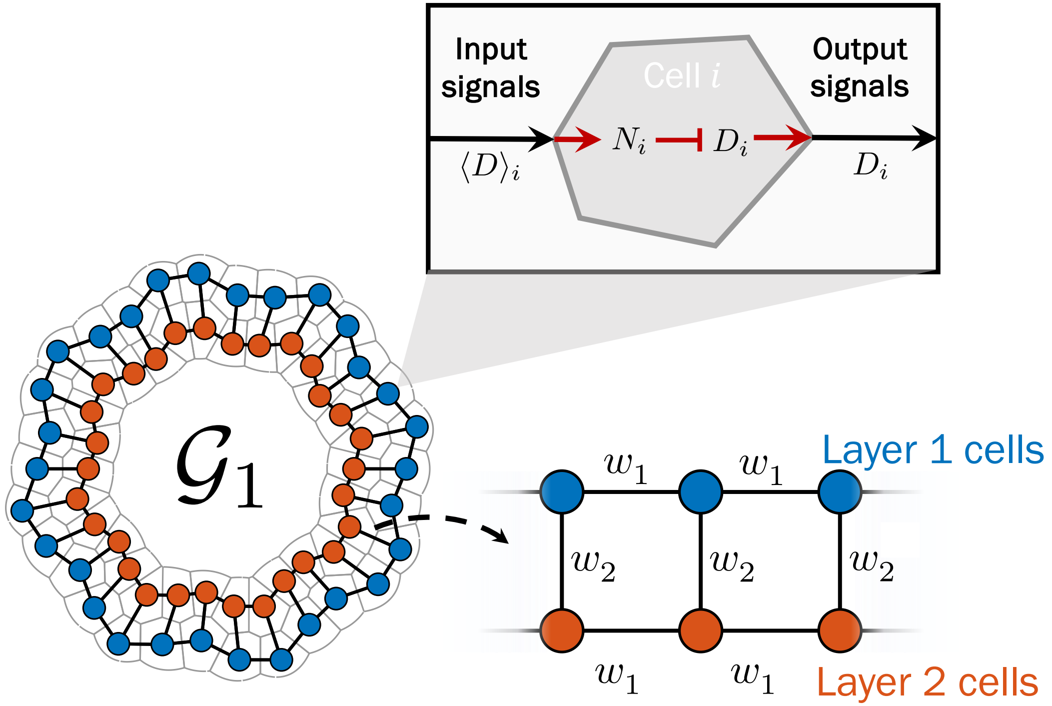
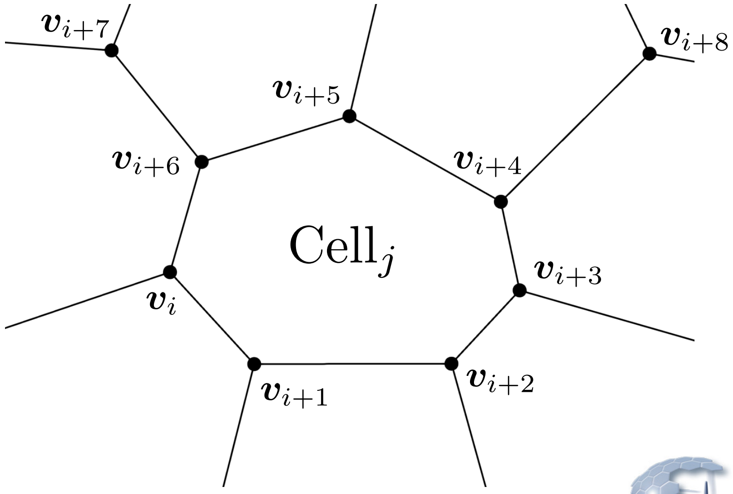


Spatially static

❶ Calibrating polarity control

② Calibrating network regimes

Cell-based modelling



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Calibrating polarity control

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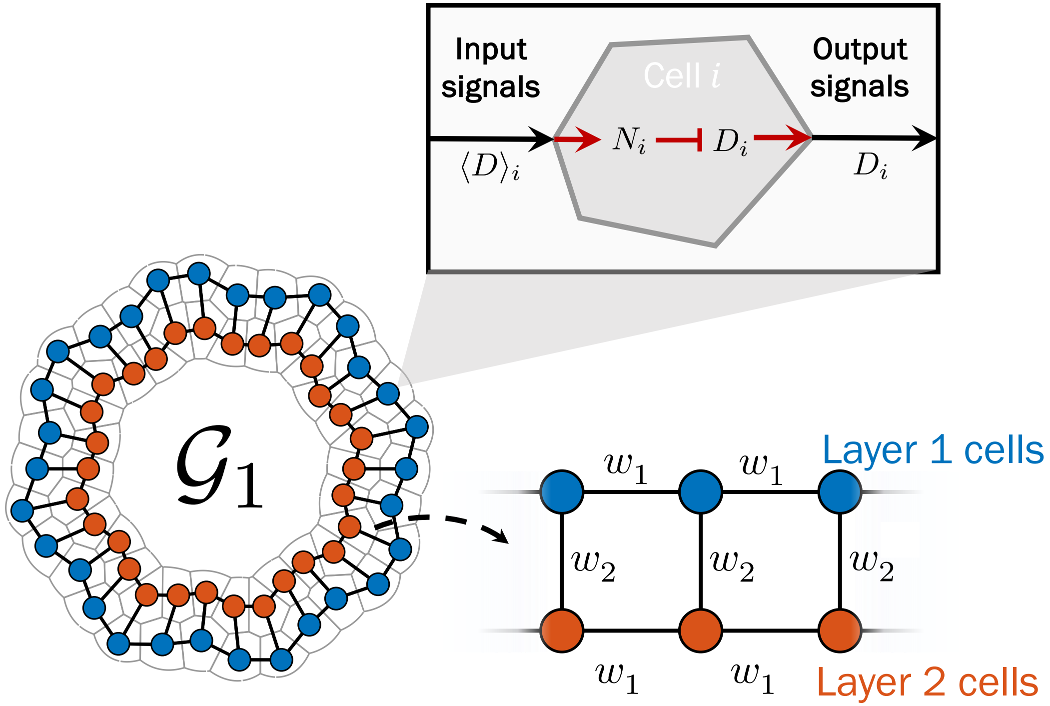
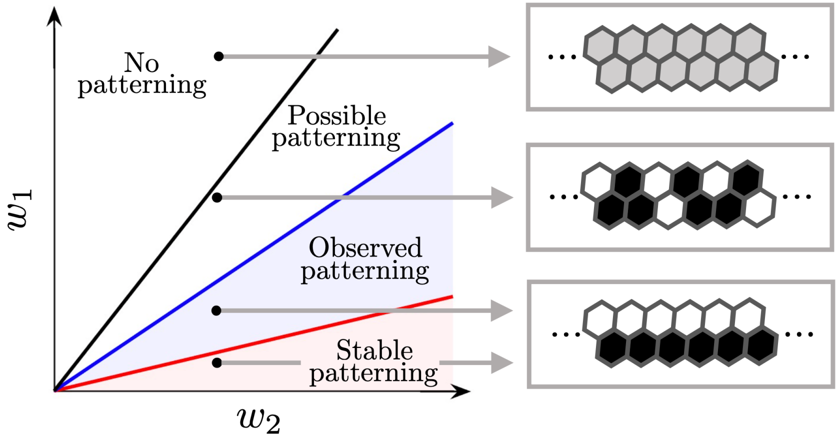


Network quotienting
+
Monotone ODE theory
+
Control theory

Conditions for stable laminar patterns with lateral-inhibition



$$\boxed{\frac{w_1}{w_2} < \alpha \frac{n_{cross}}{n_{same}} < 1}$$

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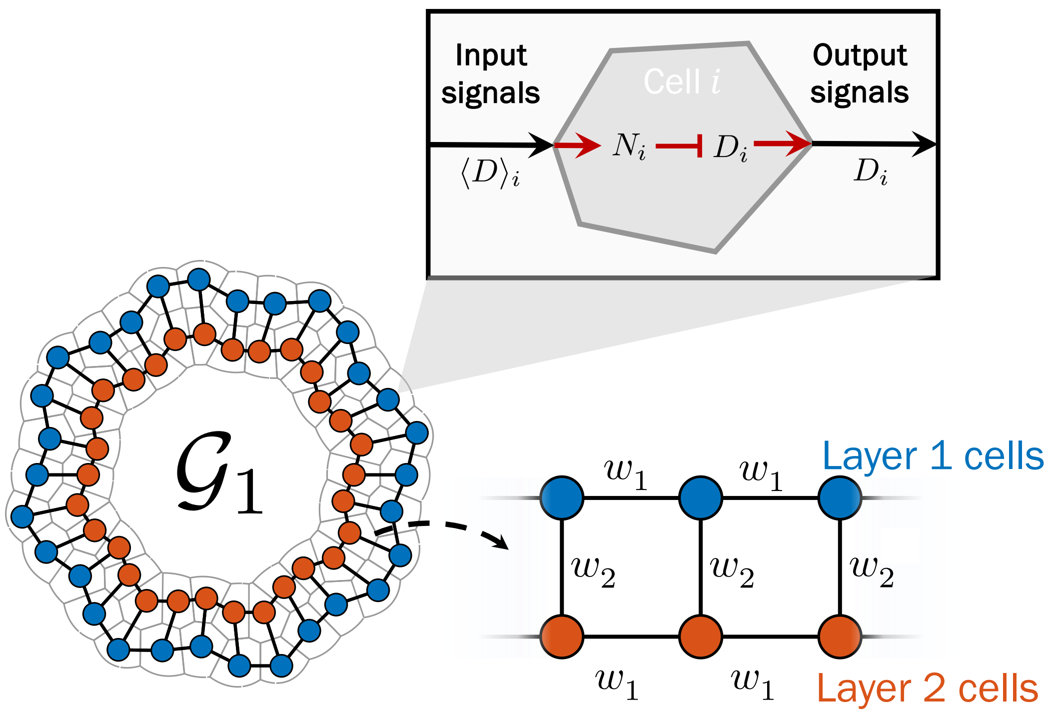
Calibrating polarity control

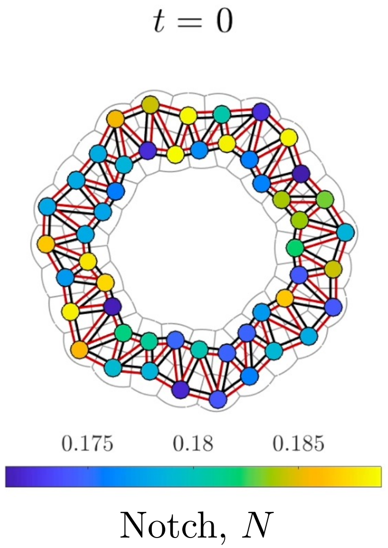
Network coupled ODEs (IO systems)



Network quotienting
+
Monotone ODE theory
+
Control theory

Conditions for stable laminar patterns with lateral-inhibition

$\alpha = 0.11$
$n_{same} = 2$
$n_{cross} = 2$



$\frac{w_1}{w_2} = 0.1$

$$\boxed{\frac{w_1}{w_2} < \alpha \frac{n_{cross}}{n_{same}} < 1}$$

But what about spatially dynamic domains?

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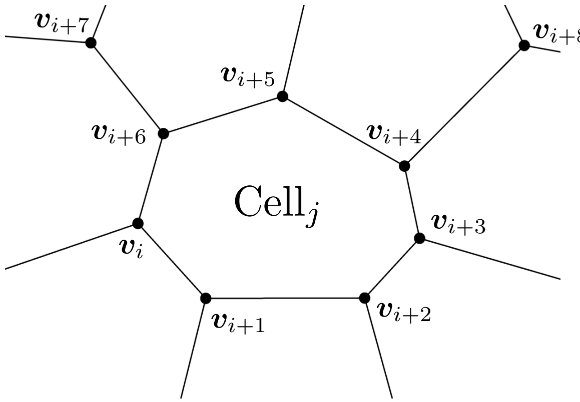
Simulating growing bilayers

Vertex model



- Cells are represented by non-overlapping polygons
- Vertices of the cells are free to move in 2D-space
- Vertices move due to external and internal forces

Cell shape is important for contact-based patterning!

Forces

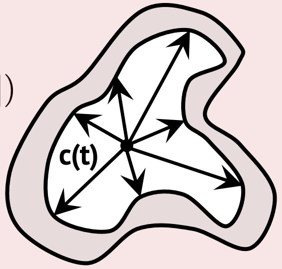
$$\boldsymbol{F}_{i,tot} = \boxed{\boldsymbol{F}_{i,NH}} + \boxed{\boldsymbol{F}_{i,LP}} + \boxed{\boldsymbol{F}_{i,rnd}}$$

Nagai-Honda:

$$\boldsymbol{F}_{i,NH} = -\nabla_i \sum_{k\in\mathcal{N}_i} \left(\underbrace{a\left(A_k - A_{0_k,}\right)^2}_{\text{Cell area}} + \underbrace{c\left(C_k - 2\sqrt{\pi A_{0_k}}\right)^2}_{\text{Cell perimeter}} + \underbrace{\sum_{j=0}^{n_k-1} b_{k,j} d_{k,j}}_{\text{Cell-cell adhesion}} \right)$$

Luminal pressure:

$$\boldsymbol{F}_{i,LP} = p_1 \underbrace{\frac{\boldsymbol{r}_i(t) - \boldsymbol{c}(t)}{||\boldsymbol{r}_i(t) - \boldsymbol{c}(t)||}}_{\text{Outward pressure force}} \exp\left(-p_2 ||\boldsymbol{r}_i(t) - \boldsymbol{c}(t)||\right)$$



Small spatial noise:

$$\boldsymbol{F}_{i,rnd} = \sqrt{\frac{2\xi}{\Delta t}}\boldsymbol{\nu} \qquad \boldsymbol{\nu} \sim \mathcal{N}(\boldsymbol{0}, \boldsymbol{1})$$

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Simulating growing bilayers

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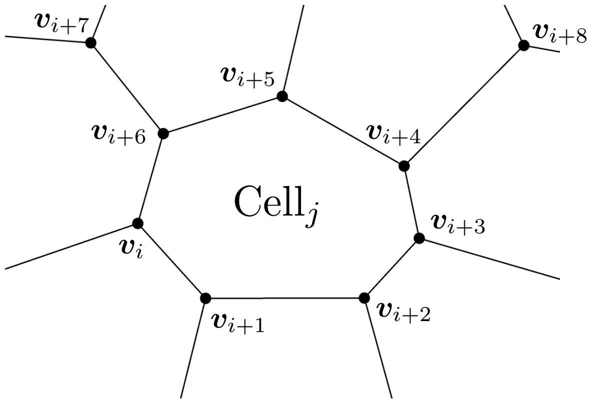

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Forces

$$\boldsymbol{F}_{i,tot} = \boldsymbol{F}_{i,NH} + \boldsymbol{F}_{i,LP} + \boldsymbol{F}_{i,rnd}$$

First-order vertex dynamics:

$$\eta \frac{d\boldsymbol{r}_i}{dt} = \boldsymbol{F}_{i,tot}$$

where $\mathbf{r}_i$ is the position of vertex $\mathbf{v}_i$.

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Simulating growing bilayers

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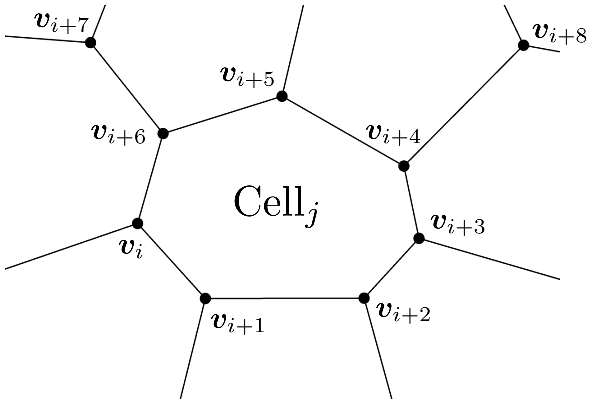

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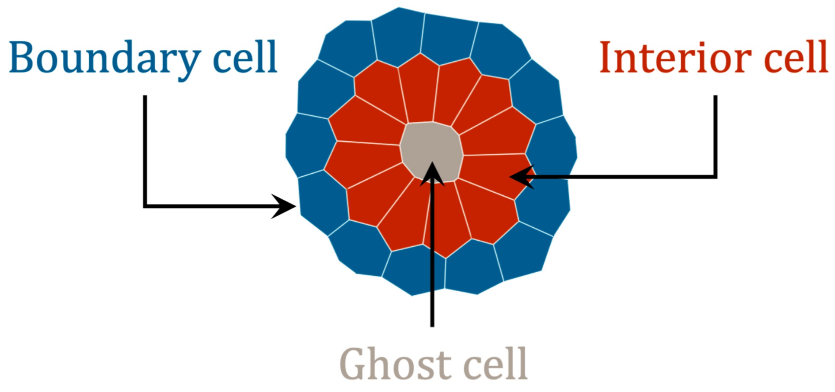
Cell-types



Boundary cells (basal cells):
- If cell is on the boundary

Interior cells (luminal cells):
- If cell is on not the boundary

Ghost cells (lumen - terminal):
- If cell is neighbouring >5 interior cells for >3 hours

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Simulating growing bilayers

Forces

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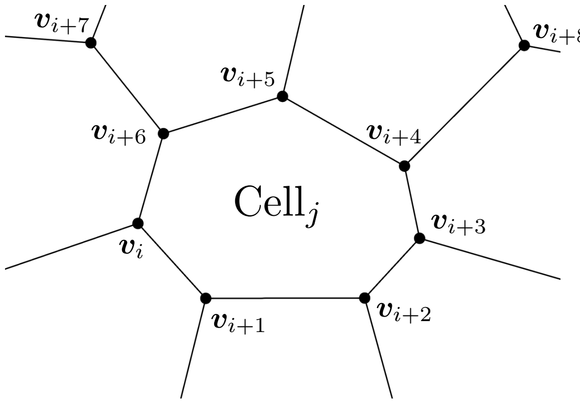
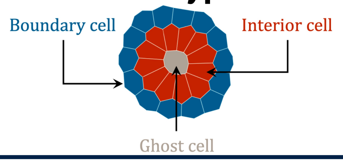
Vertex model



Cell-types



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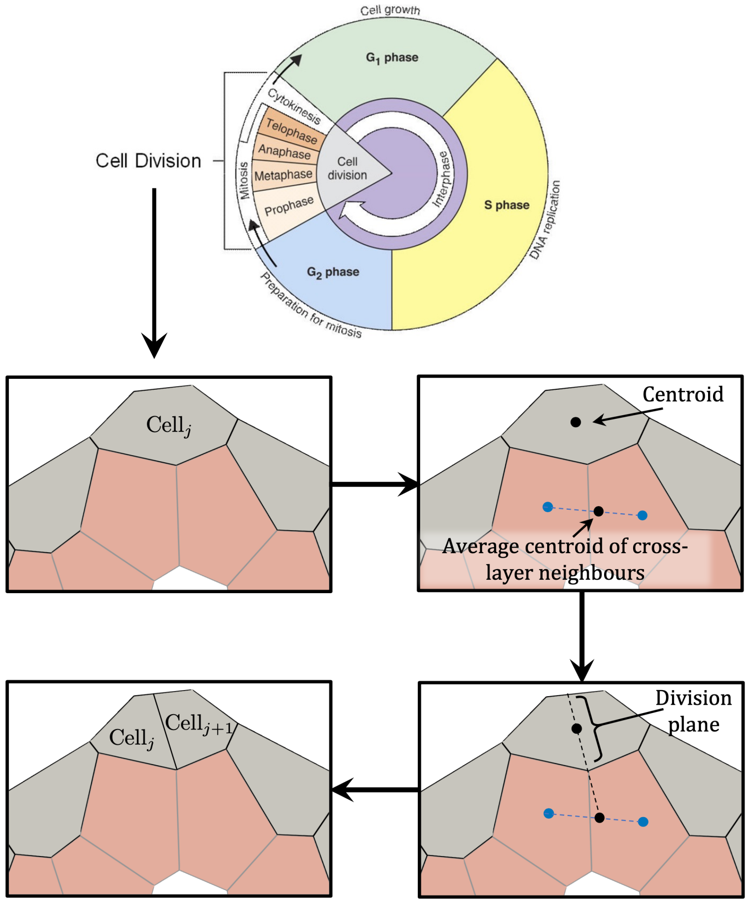
Cell shape is important for contact-based patterning!

Apical-basal division



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Simulating growing bilayers

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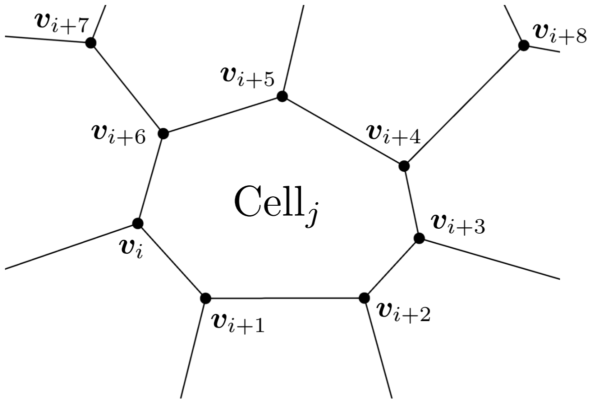
Vertex model



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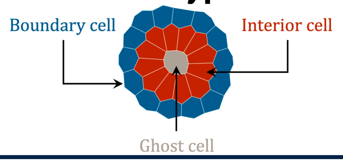

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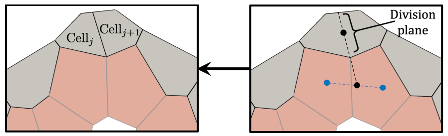

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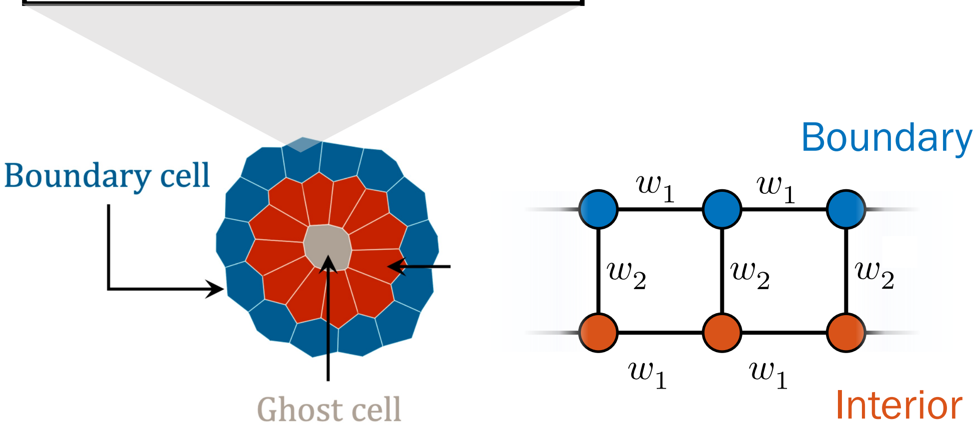
Cell shape is important for contact-based patterning!

Polarity-dependent Notch signalling

Collier Notch-Delta model

$$\frac{dN_i}{dt} = \frac{\langle D \rangle_i^k}{\alpha + \langle D \rangle_i^k} - N_i$$

$$\frac{dD_i}{dt} = \frac{1}{1 + \beta N^h} - D_i$$



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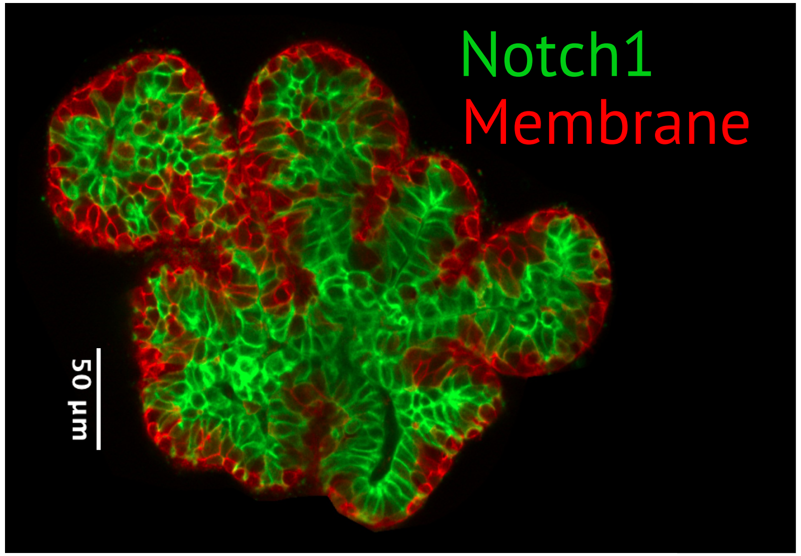
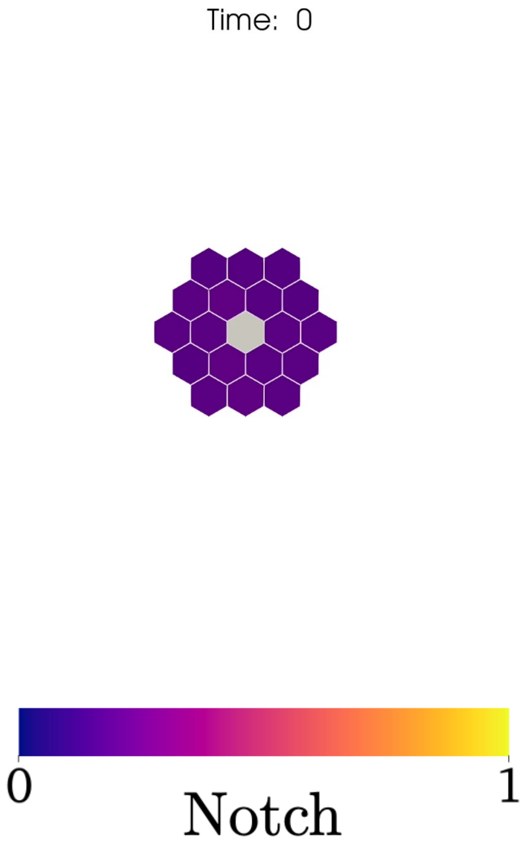
Laminar patterning in growing bilayers





Globally fixed polarity weights for hexagonal grid

$$\boxed{\frac{w_1}{w_2} < \alpha \frac{n_{cross}}{n_{same}} < 1} \implies \frac{w_1}{w_2} < 0.11$$

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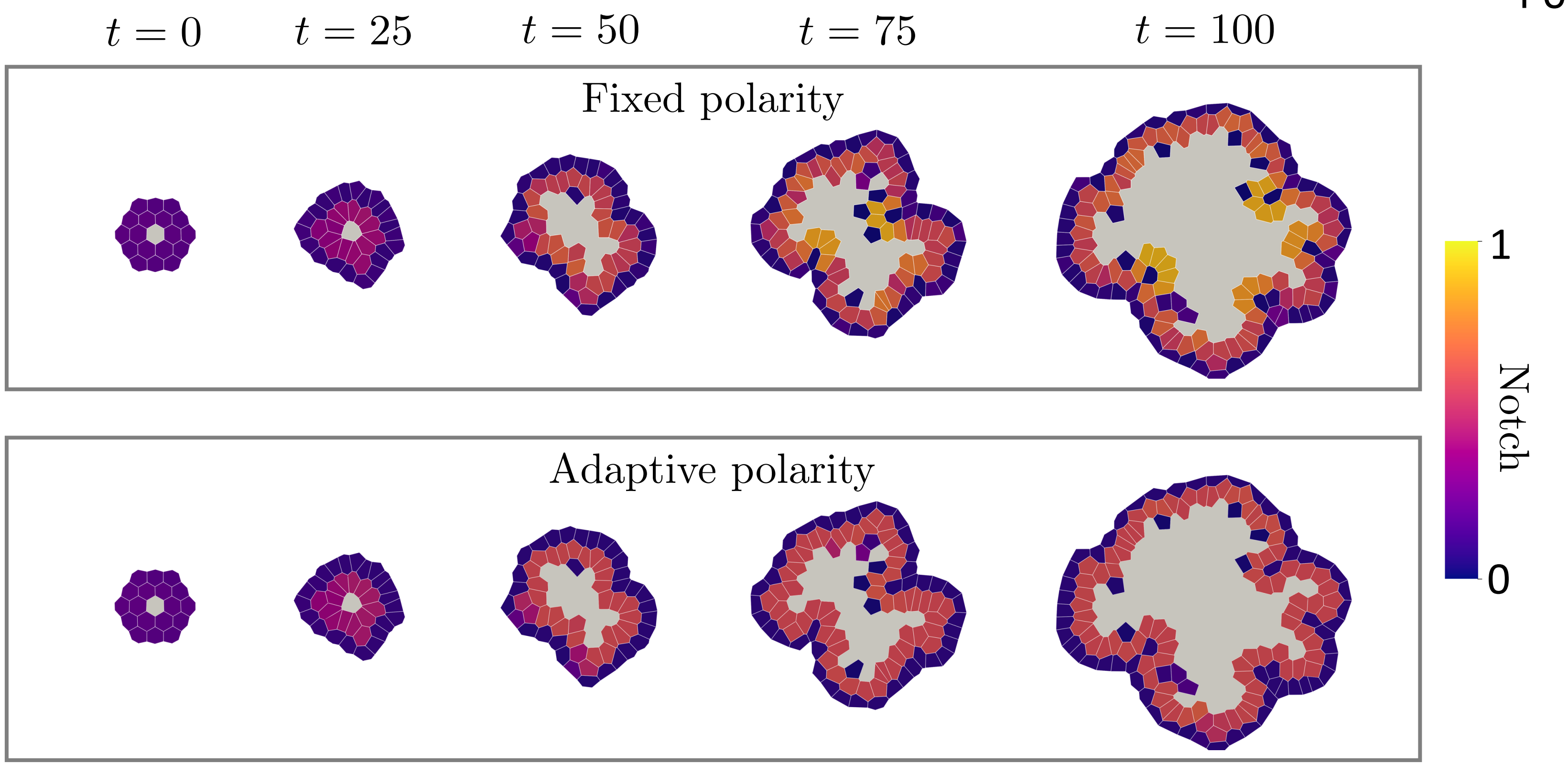
Globally fixed polarity weights for hexagonal grid

$$\boxed{\frac{w_1}{w_2} < \alpha \frac{n_{cross}}{n_{same}} < 1} \implies \frac{w_1}{w_2} < 0.11$$

Adaptive polarity weights from cell contacts

$$\boxed{\frac{w_1}{w_2} < \alpha \frac{n_{cross}}{n_{same}} < 1} \implies \frac{w_1^{[i]}}{w_2^{[i]}} < 0.11 \frac{n_{cross}^{[i]}}{n_{same}^{[i]}}$$

For each cell$_i$



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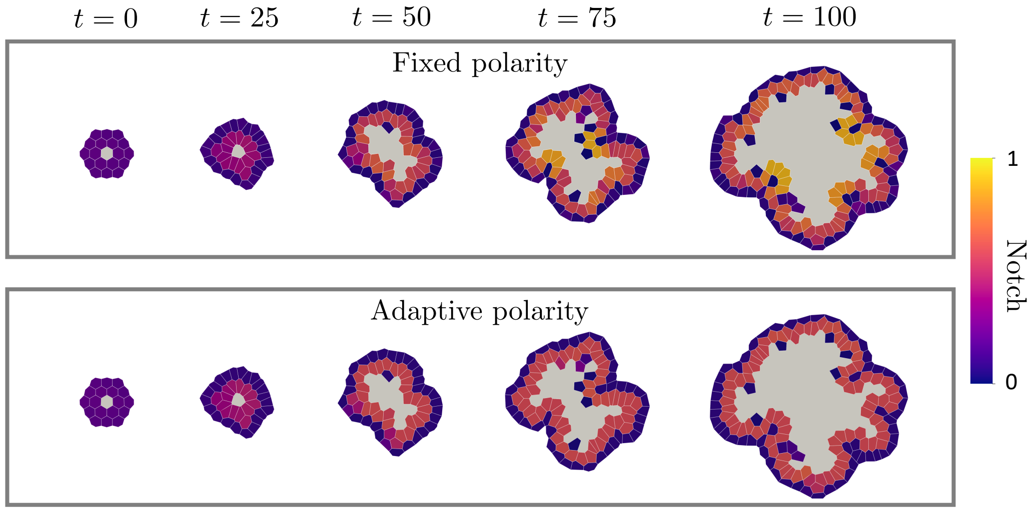

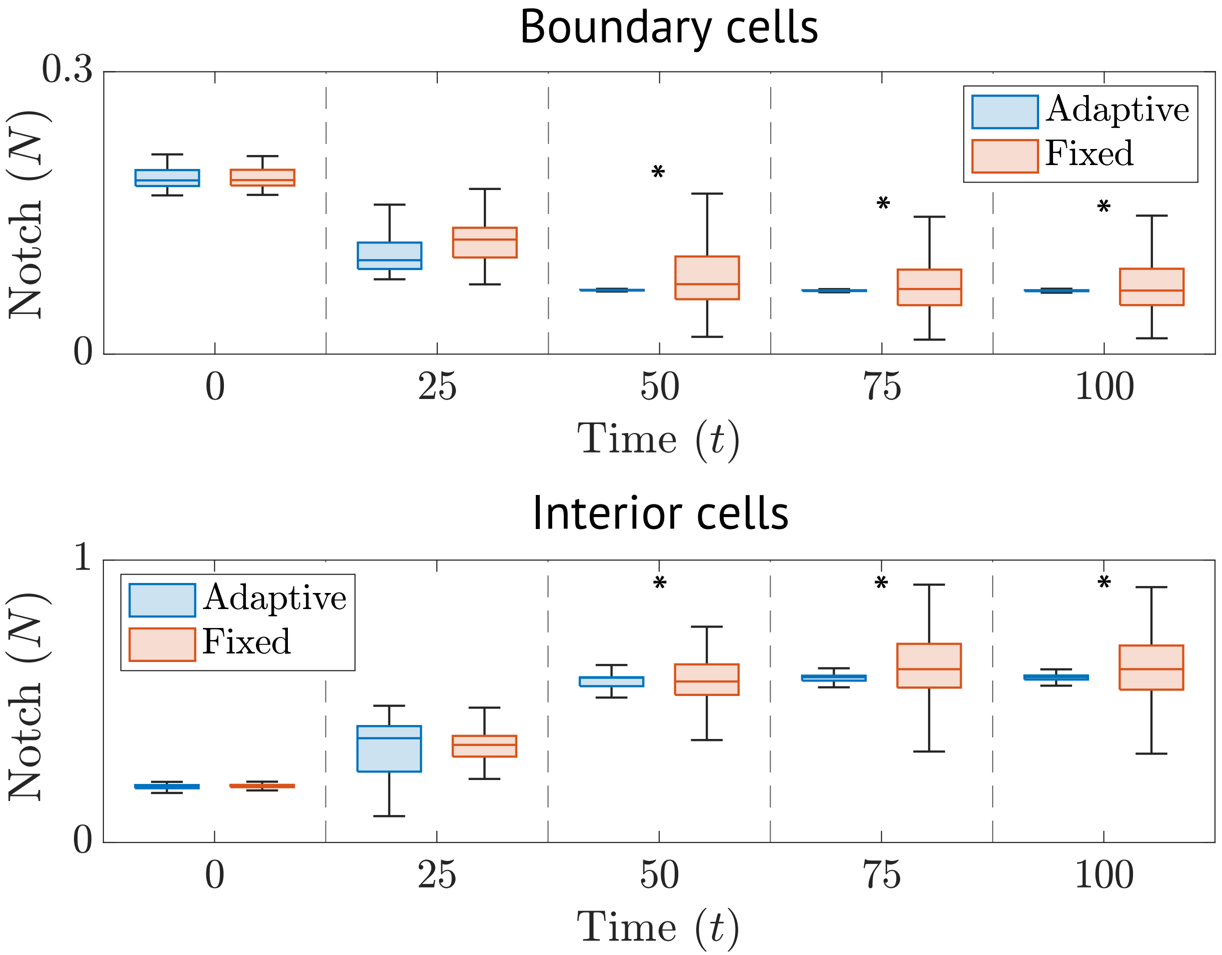

Insights

1. Laminar patterns of Notch can be generated from a simple polarity model.
2. Adaptive polarity provides an additional pattern-stabilising mechanism.

Summary statistics over 10 simulations for each mech. * denotes p<0.01 in Ansari-Bradley variance test.

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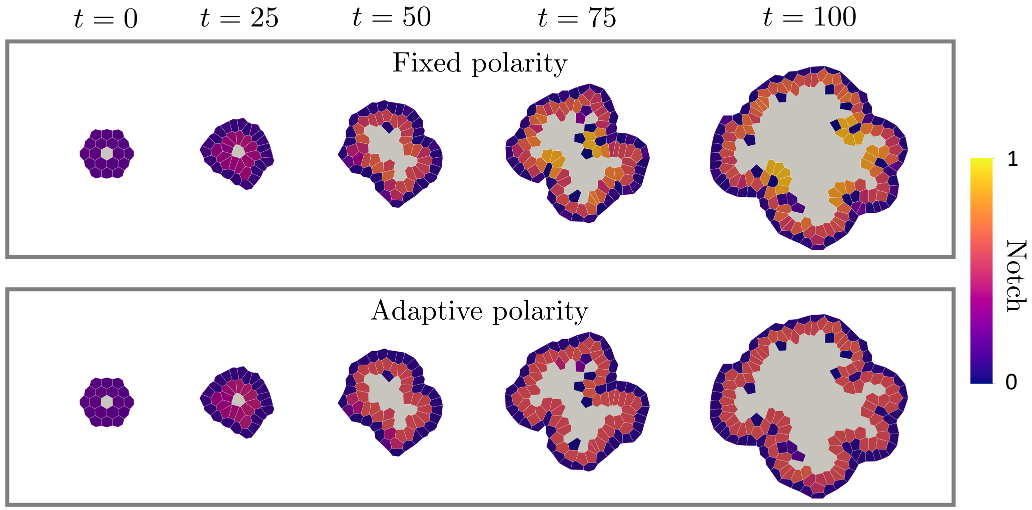
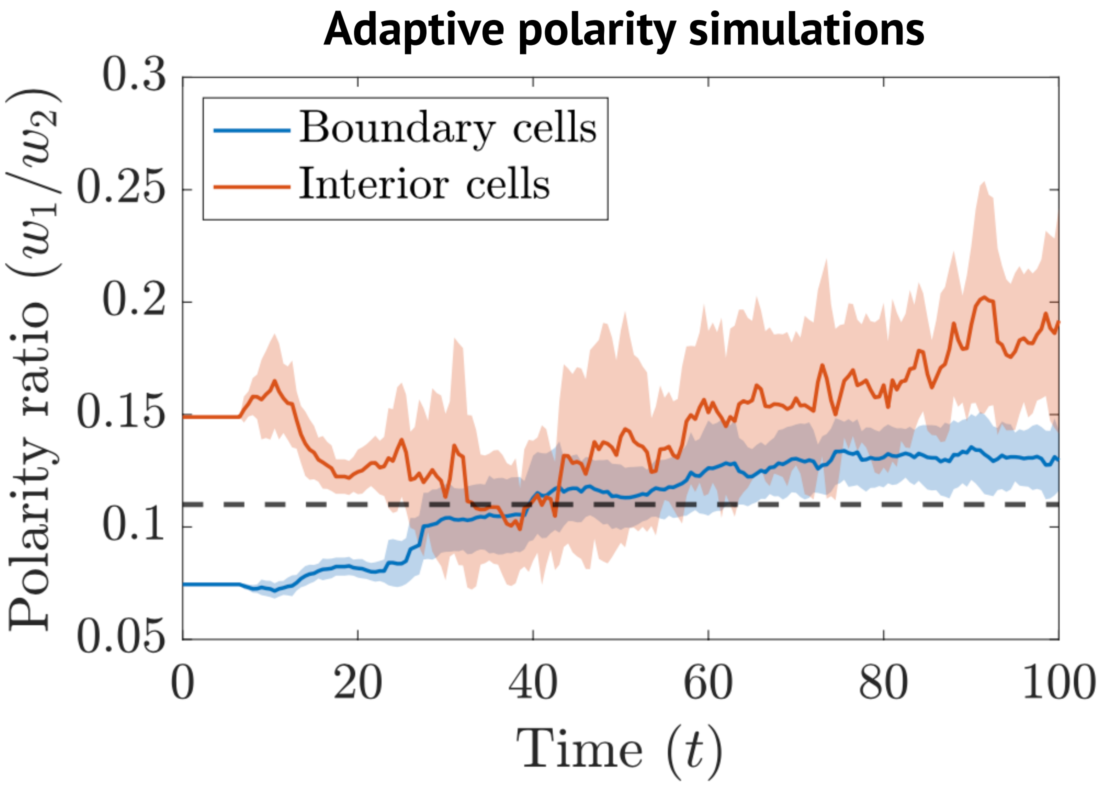
Laminar patterning in growing bilayers





Insights

1. Laminar patterns of Notch can be generated from a simple polarity model.
2. Adaptive polarity provides an additional pattern-stabilising mechanism.
3. Boundary (basal) cells play a more dominant role in plasticity control.

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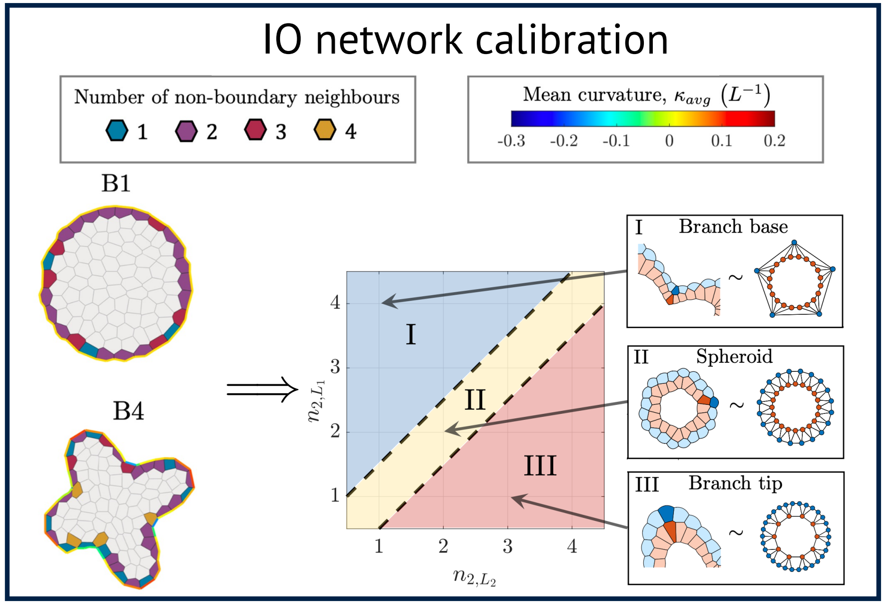
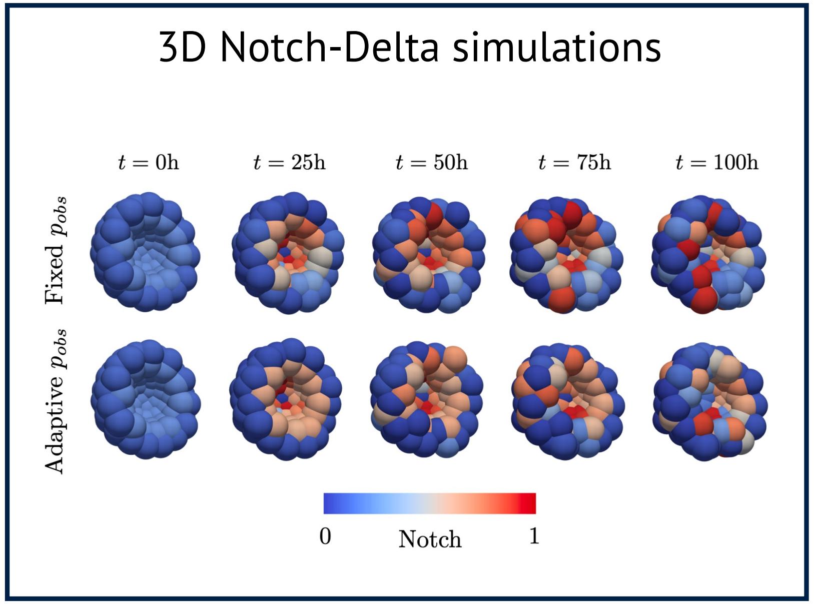
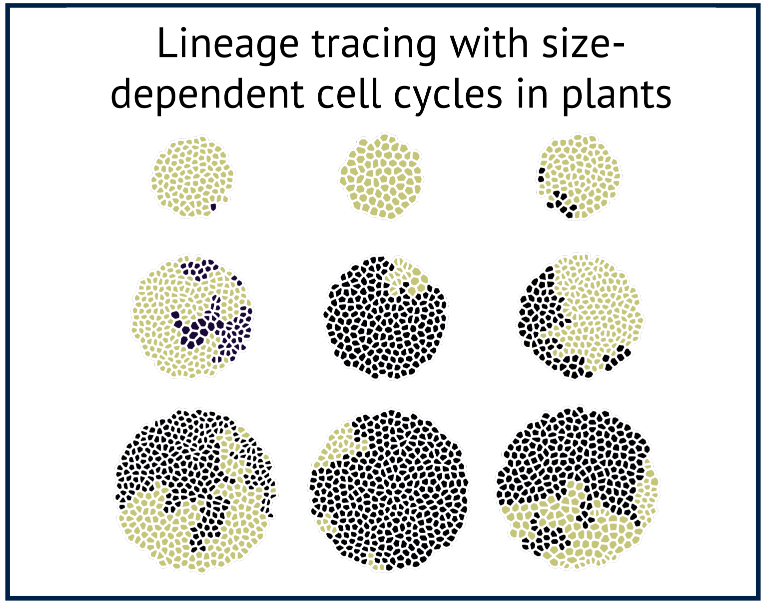
Outlook

1. Promoting polarity in mammary organoid development can stabilise laminar cell fates – *polarity mediated culture conditions*

2. Chaste is a highly versatile and powerful tool for studies in developmental biology:







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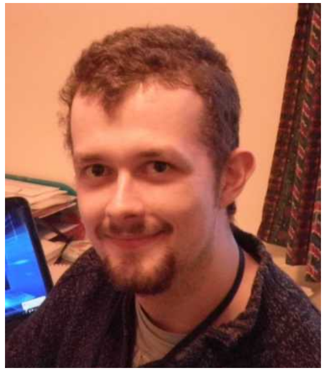
Acknowledgements

Supervisors:



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Prof. Trevor Dale

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(University of Bristol)

Dr Victoria Marsh Durban
(Cellesce)

Dr Mairian Thomas
(Cellesce)

References + code

Cellesce®

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