CELLMORPHODYNAMICS
LATINAMERICA

Course "Optics, forces & development"

Modelling Self-organisation in Developmental Biology

11 March 2024

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dfi fcfm

Menu for today

1) Important definitions

2) Discuss usefulness of physics

3) More definitions

4) Talk about tissue organisation

5) Example: modeling in branching morphogenesis
- Lineage tracing
- Tissue organisation

6) Take home message

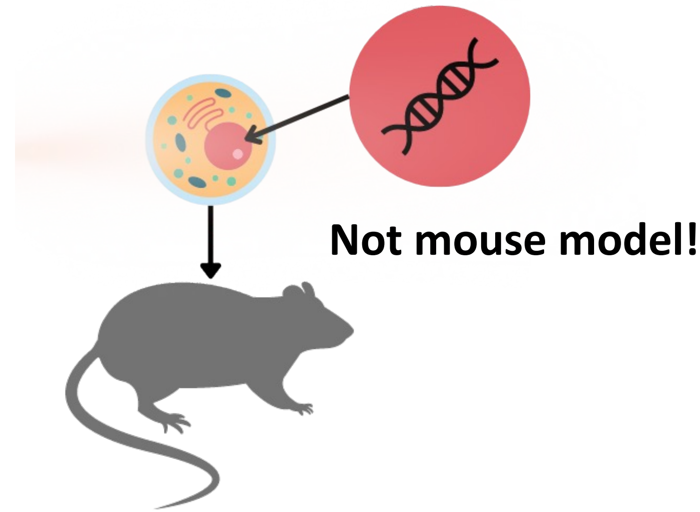
***Please feel free to interrupt at any time.**

Modelling self-organisation in Developmental Biology

Mathematical model
Representation of a system using *mathematical language.*

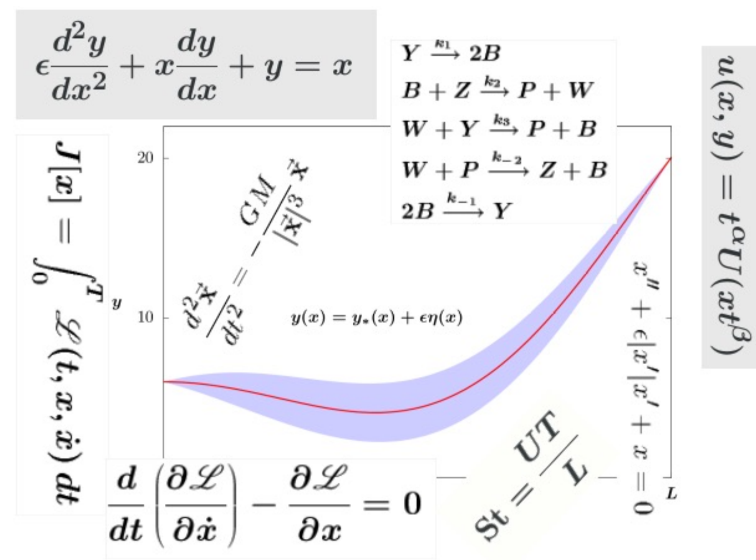
- **Biophysical models** (mathematical/physical models applied to biology) often *incorporate physical and chemical principles* to understand and predict biological phenomena, such as the behavior of cells, organs, or entire organisms.

A *good* model should have
1) *Consistency* with available data
2) *Simplicity*: contain as few free parameters as possible.
3) *Predictive power*: should be able to make testable predictions.



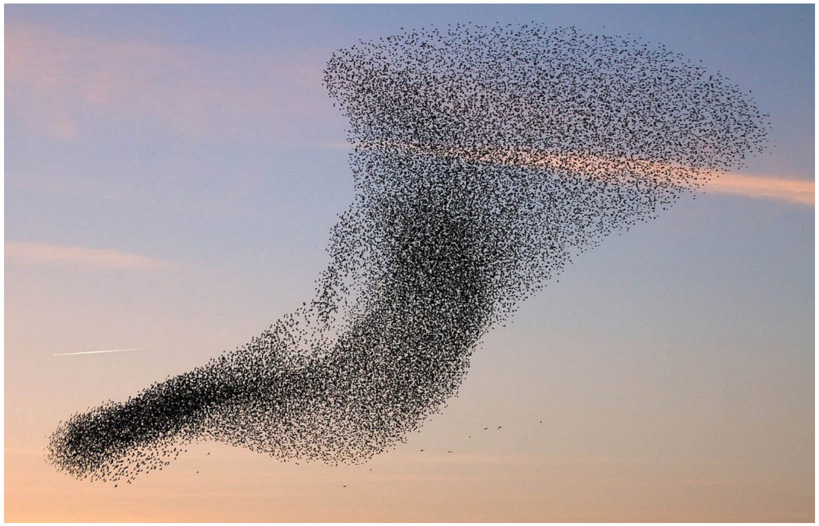
Not mouse model!

Mathematical/biophysical model!



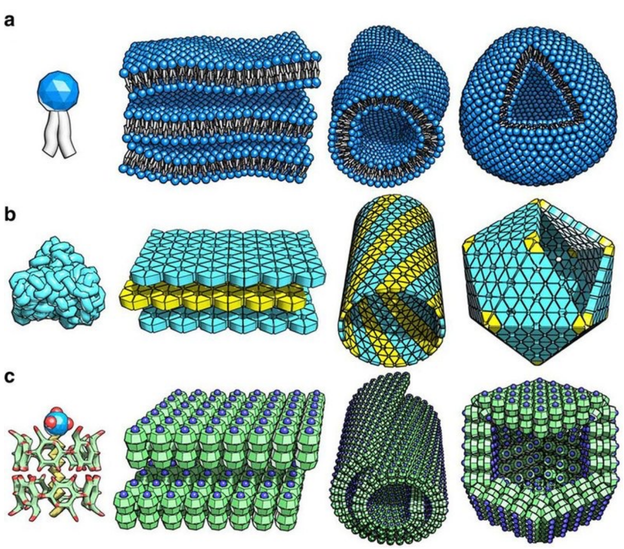
Modelling **self-organisation** in Developmental Biology

[Credit: Aditya Ananthram]

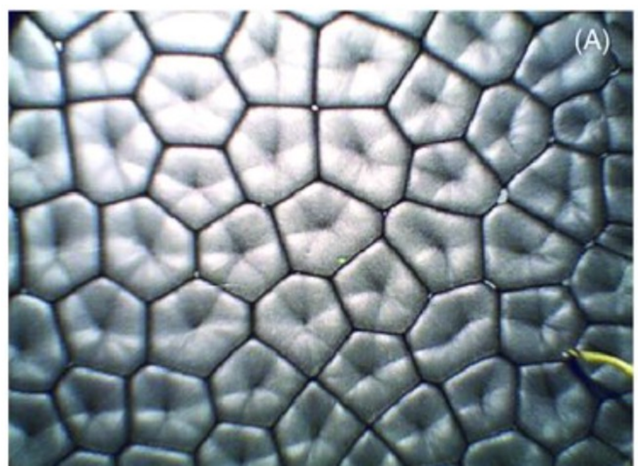


Self-organisation (in biology)
Refers to the process by which structures, patterns, or behaviours emerge spontaneously within biological systems without external direction. This phenomenon is observed at various levels of biological organization, from molecular and cellular to organismal and ecological scales.

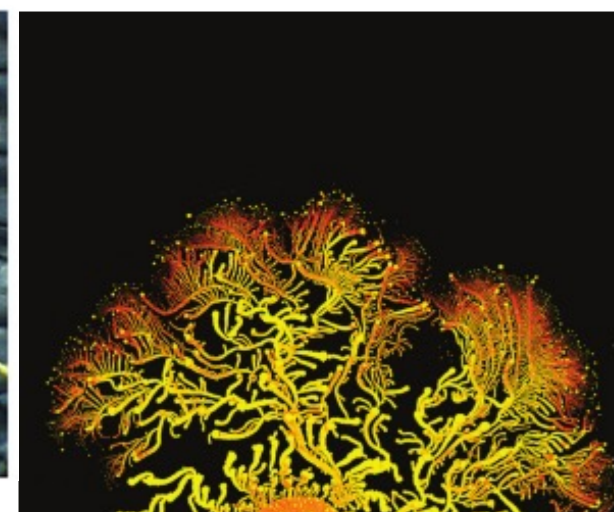
[Yang et al. (2017)]



[Maroto et al (2007)]

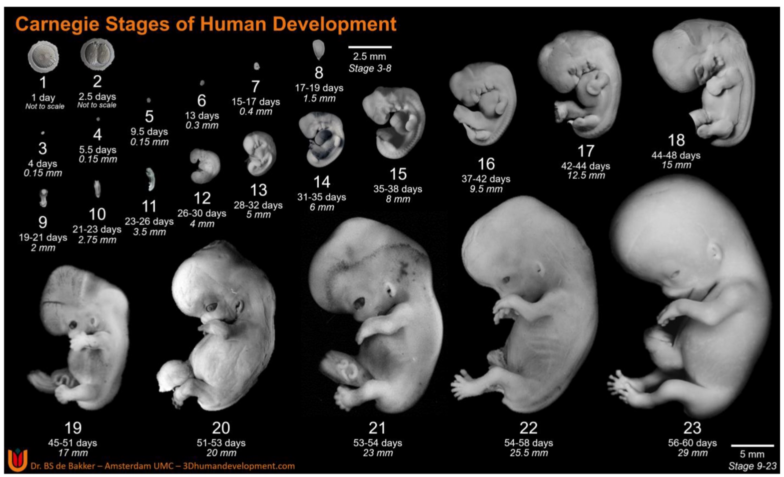


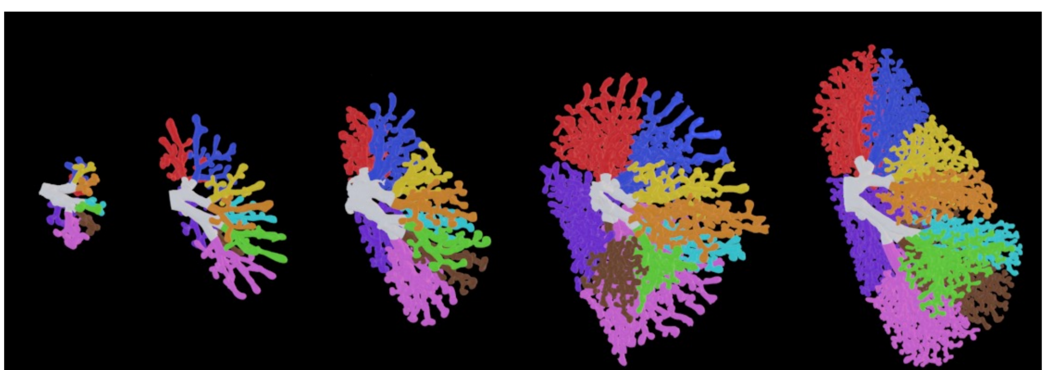
[Credit: Eshel Ben-Jacob]

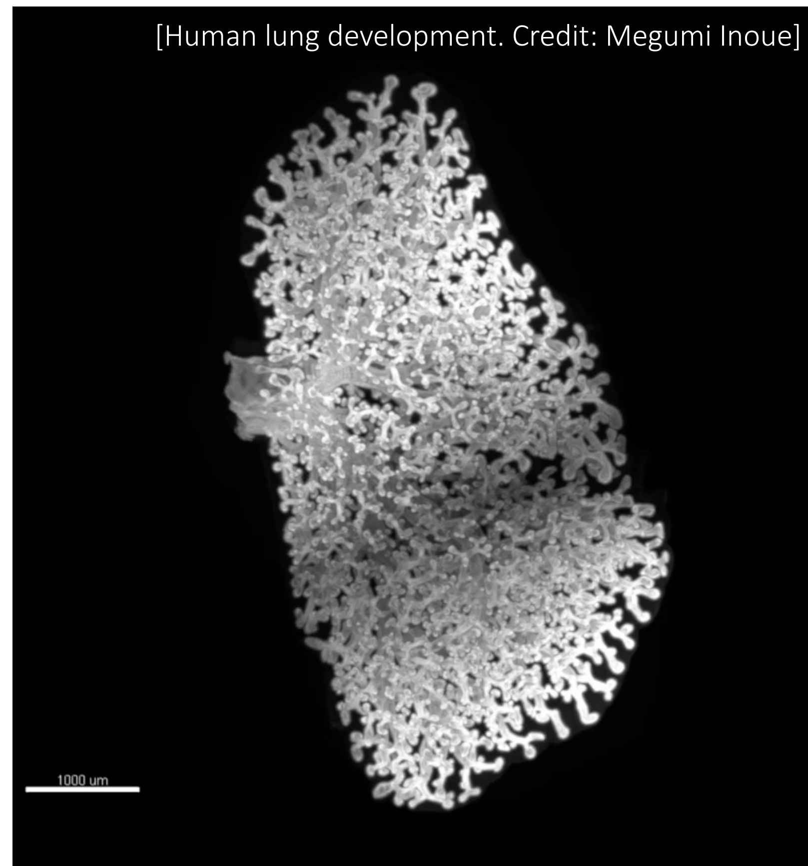


Modelling self-organisation in **Developmental Biology**

Developmental biology
is the study of how organisms grow and develop from a single cell into a complex organism. It explores the genetic, molecular, cellular, and environmental factors that control these processes, including cell differentiation, tissue formation, and organ development. Developmental biologists aim to understand the *underlying mechanisms* and how they are influenced by various factors.

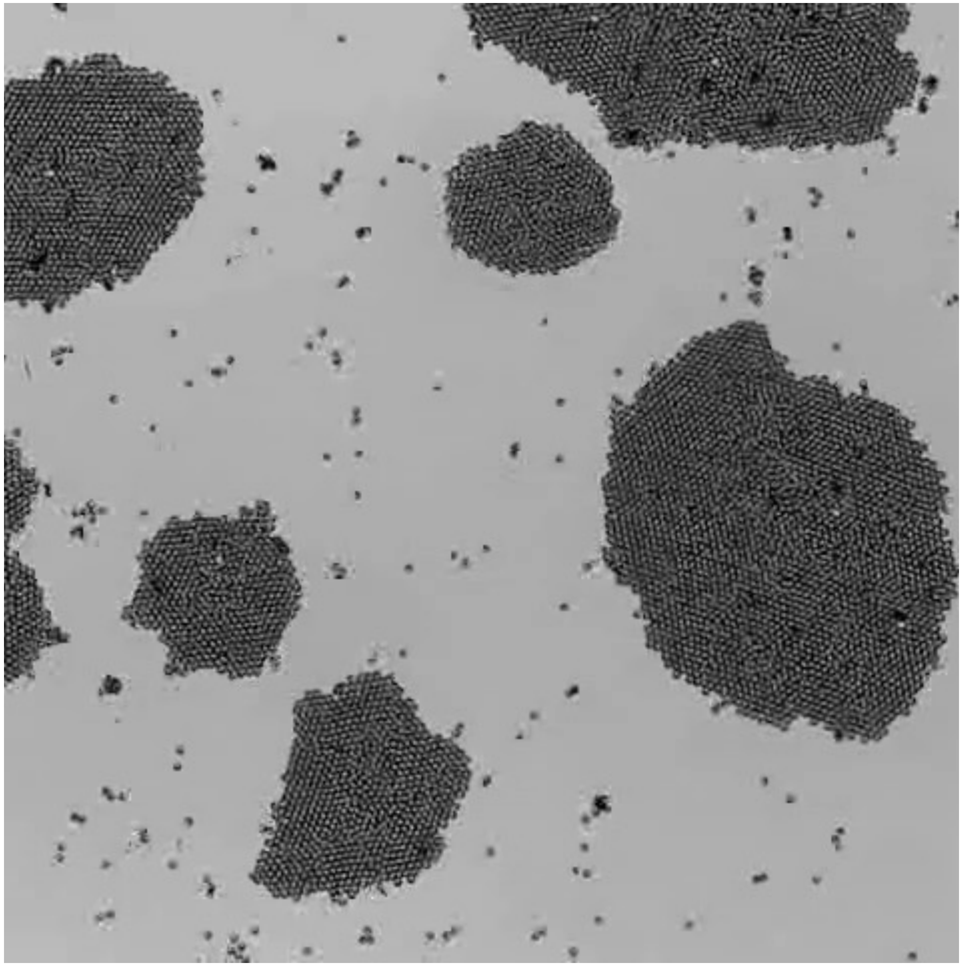





[Human lung development. Credit: Megumi Inoue]

[Imperial College - Human Embryo Development (video)]

But why do we even need physics/maths for?

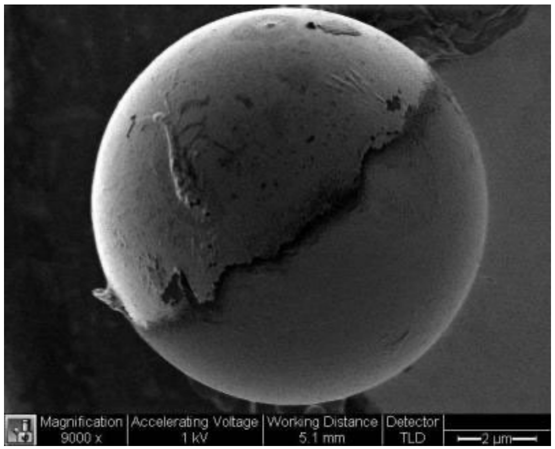


Phys. Rev. Lett. **123**, 098001 (2019)

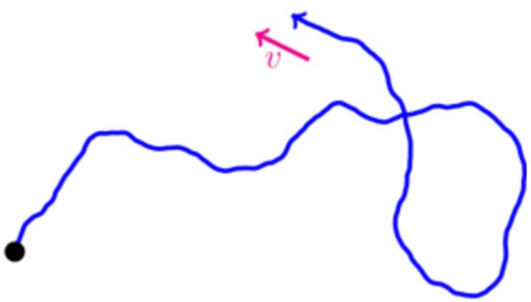
Cates (2012)
Marchetti et al. (2013)

…to extract minimal ingredients

Janus particles



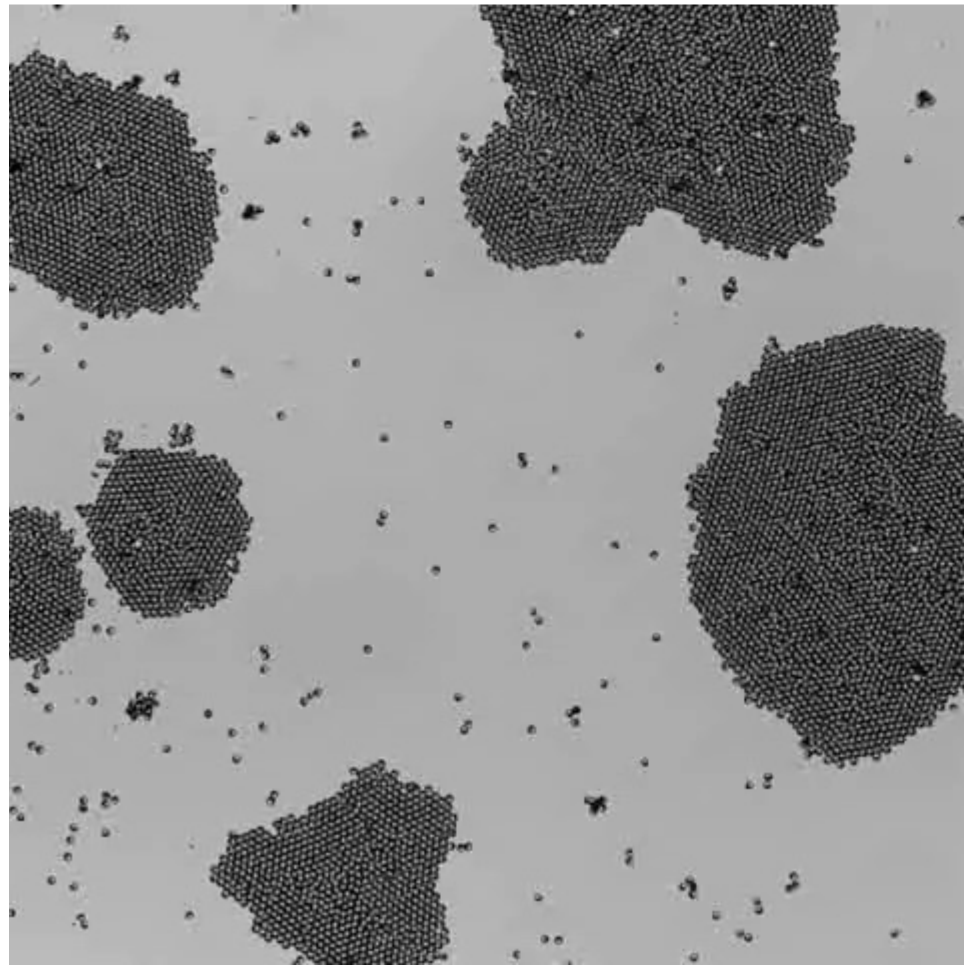
Active Brownian Motion



$$\dot{x} = v \cos\theta + \xi_x$$

$$\dot{y} = v \sin\theta + \xi_y$$

$$\dot{\theta} = \xi_\theta$$

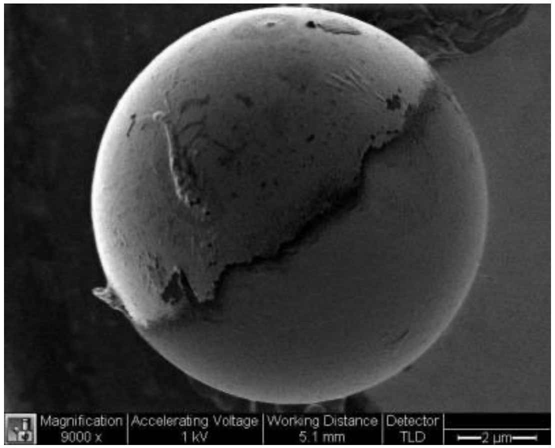


Phys. Rev. Lett. **123**, 098001 (2019)

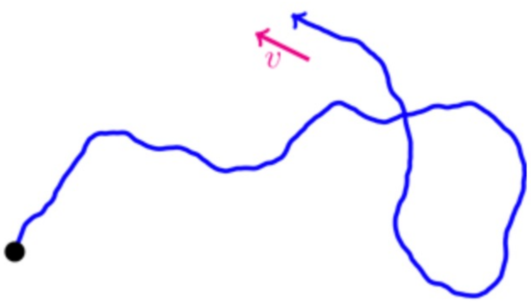
Cates (2012)
Marchetti et al. (2013)

Motility-induced pase separation (MIPS)

Janus particles



Active Brownian Motion



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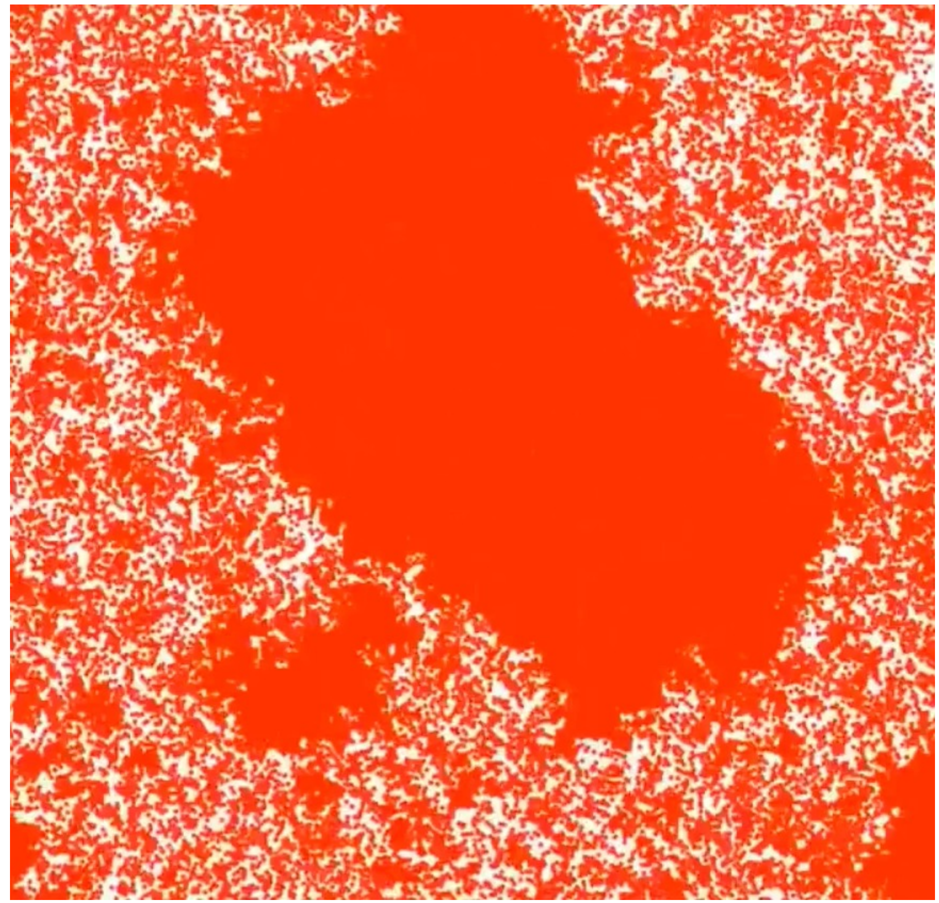
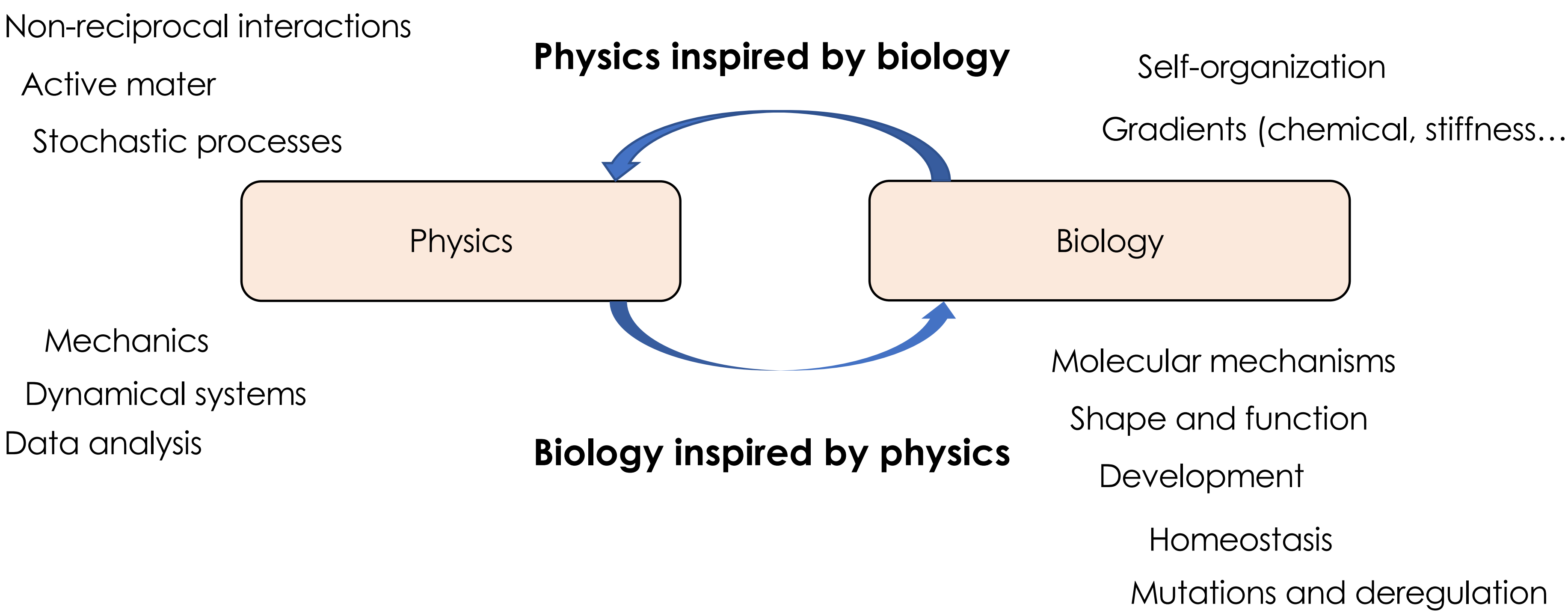


[Credit: A. Solon}

No attractive forces are needed to explain the observed phenomena!

Cates (2012)
Marchetti et al. (2013)



Note: To make the most out of your collaboration with a (bio)physicist, try to involve them as early as possible in the project!

Levels of (mathematical) description

small

Molecular: protein/DNA folding, molecular motors…

Sub-celular: gen regulation, intracelular transport processes, organelle formation and self-organisation…

Single cell: behaviour, movement, sensing, guidance…

Tissue: Spatial and temporal organisation, interactions (cell-cell, cell-substrate,…), mechanics, homeostasis, stability…

Organ: development and organisation, cell hierarchies, function, regulation…

Organism (system): regulation, homeostasis, behaviour, evolution and development (evo-devo)…

Population level: Spatial and temporal organisation, interactions…

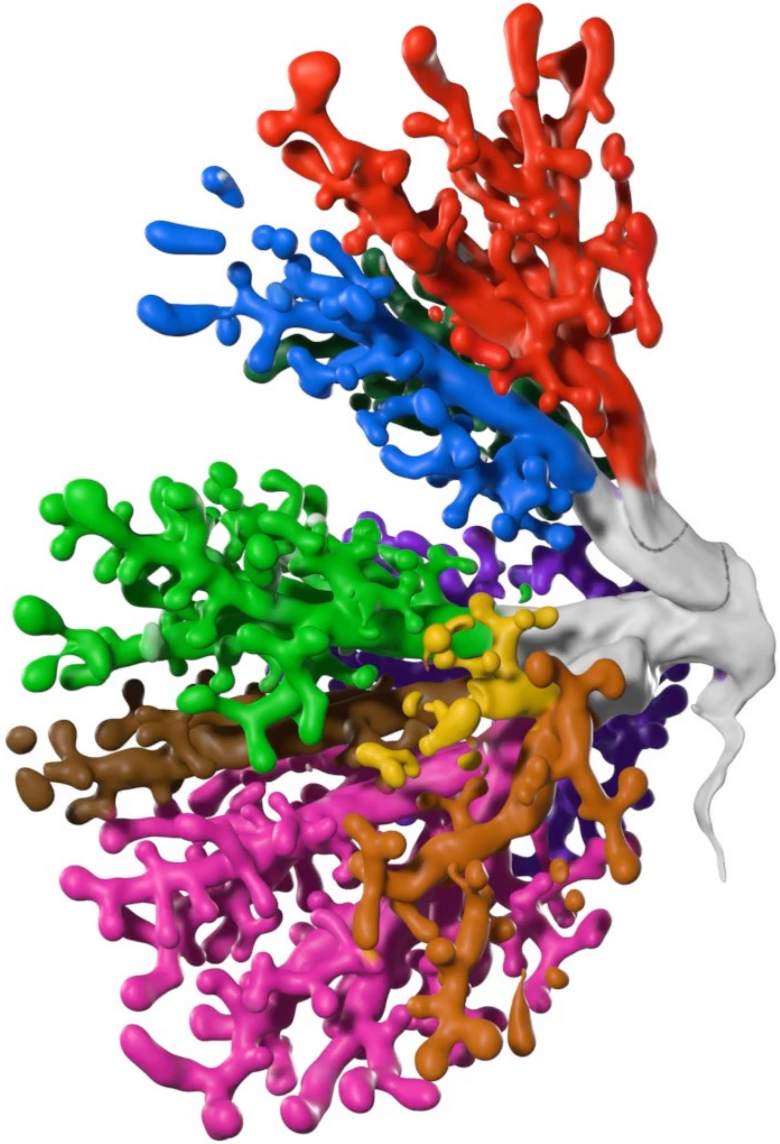
Ecosystem level: inter-species interactions, competition…

large

*Note: this is an incomplete list

With this in mind:
How can physics contribute to the understanding of development and morphogenesis?

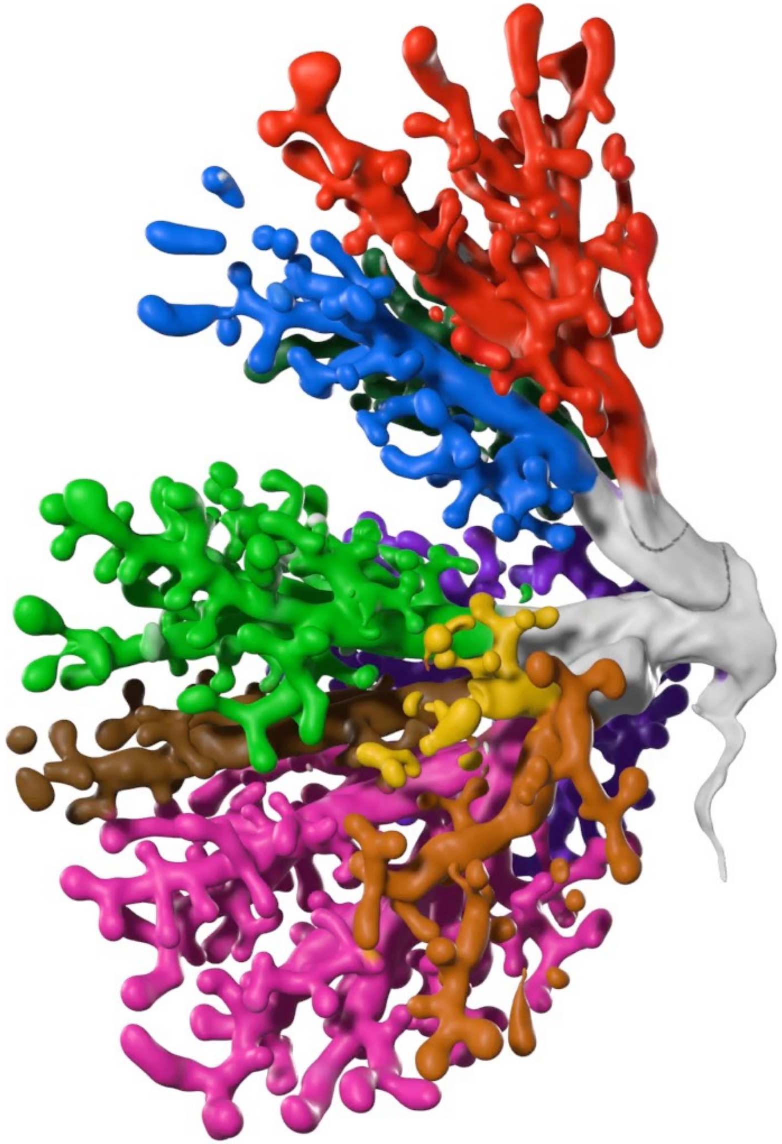
What is a cellular tissue?



Wikipedia:
"…biological materials formed by a complex and organised set of cells, of a single or various types, regularly distributed with a coordinated physiological behaviour…"

Megumi Inoue, PhD(c)
Prof Alain Chetodal
HDBI: Human Developmental Biology Initiative

What is a cellular tissue?

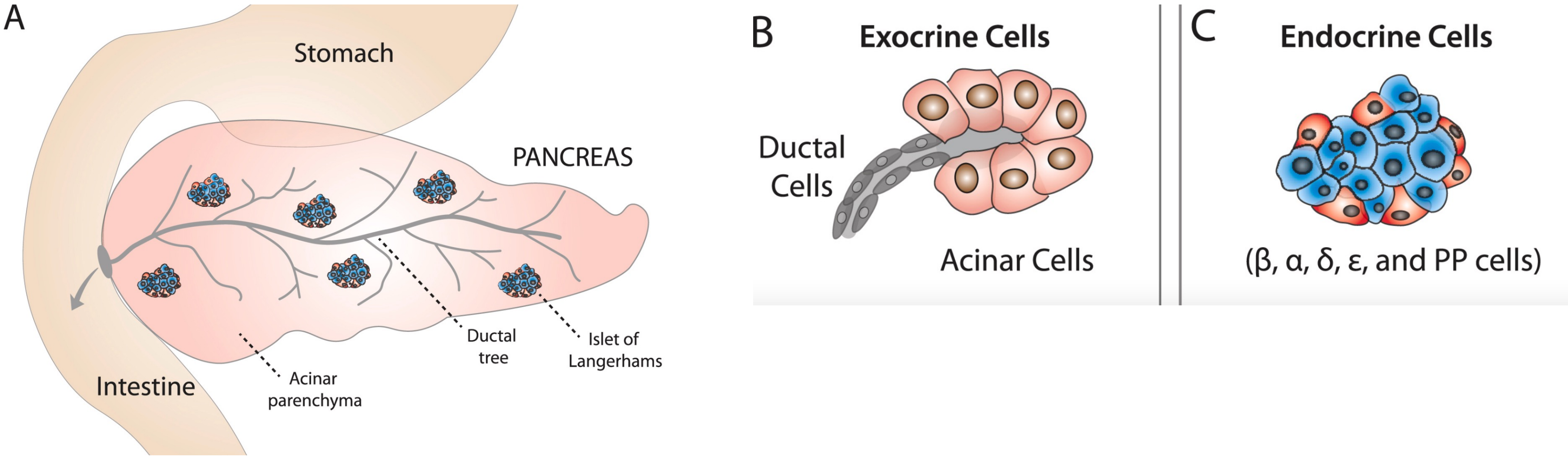


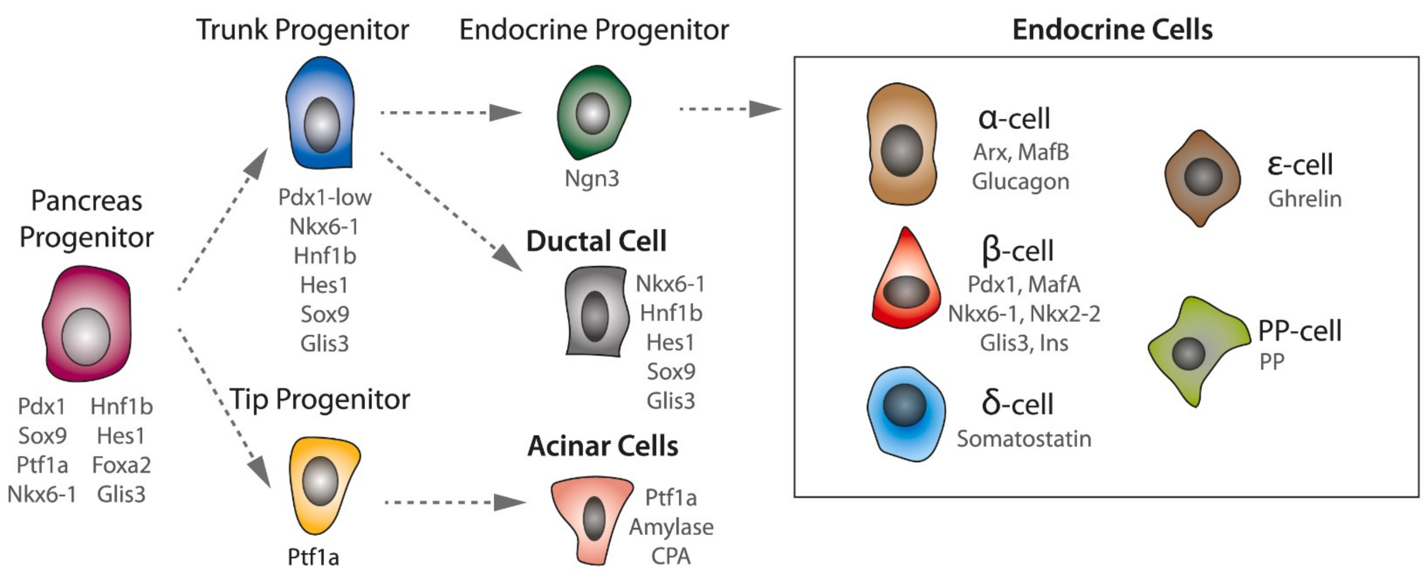
Wikipedia:
"…biological materials formed by a complex and organised set of cells, of a single or various types, regularly distributed with a coordinated physiological behaviour…"

- **How are cells in a tissue organised?**
- **How does a tissue acquire its form?**

Megumi Inoue, PhD(c)
Prof Alain Chetodal
HDBI: Human Developmental Biology Initiative

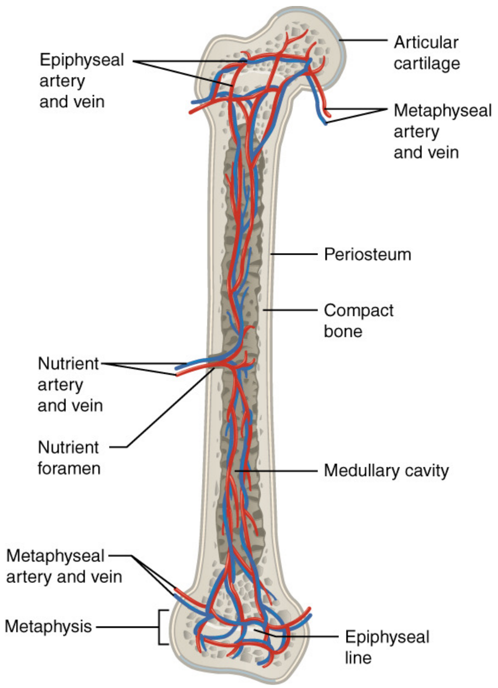
Tissues are organised in **celular hierarchies**: pancreas

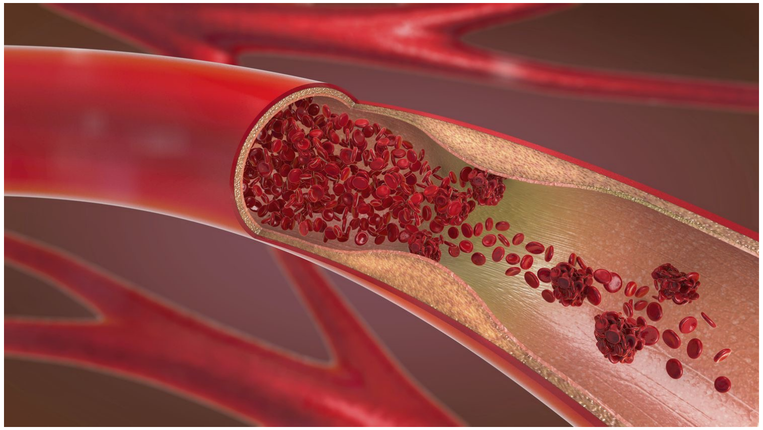


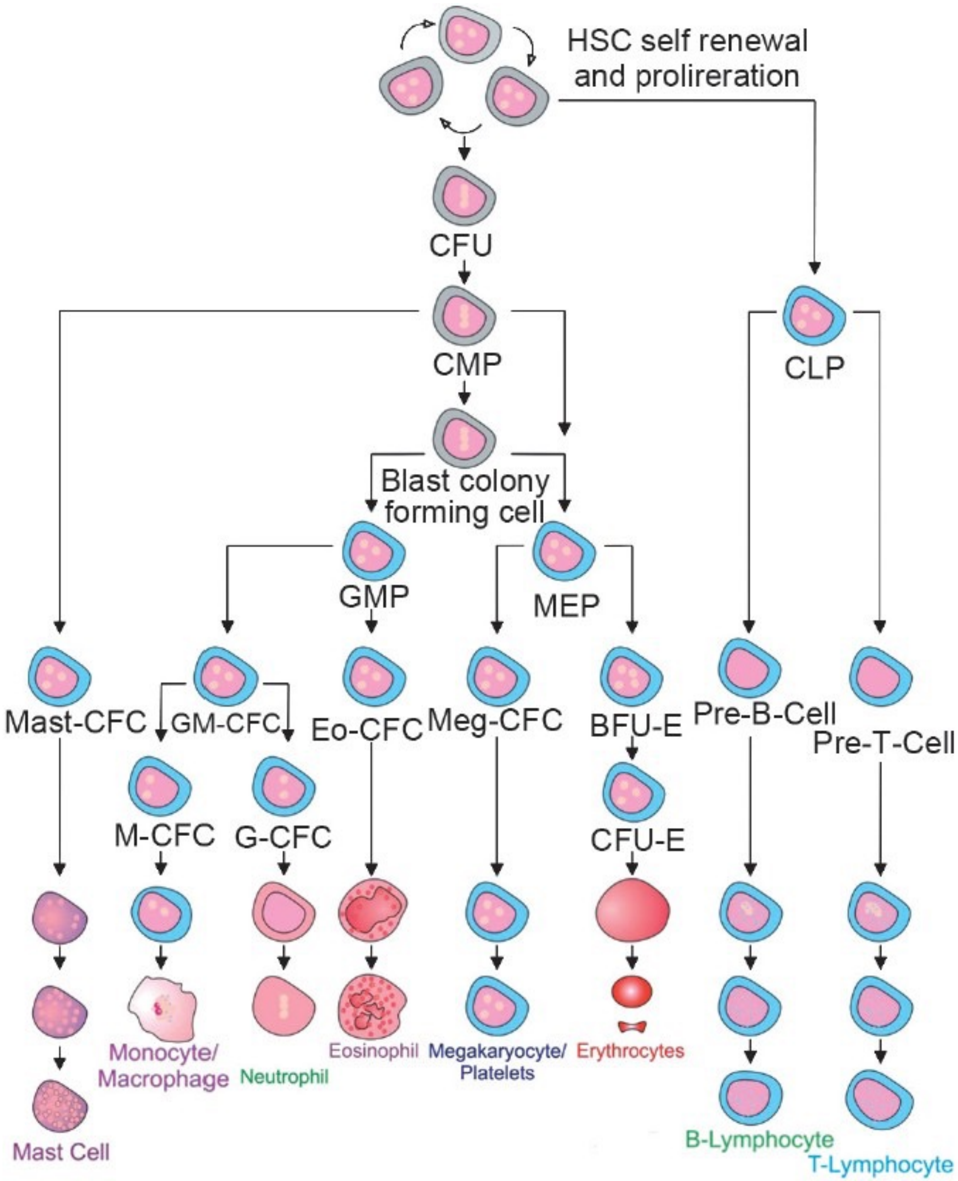


Alvares Fallas et al. Mol. Cell. Endocrinol. (2021)

Tissues are organised in **celular hierarchies**: hematopoiesis



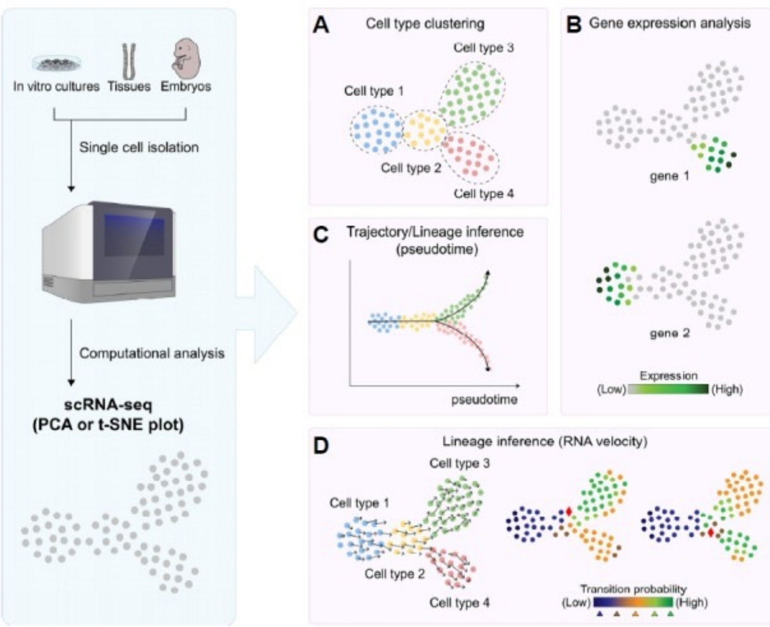


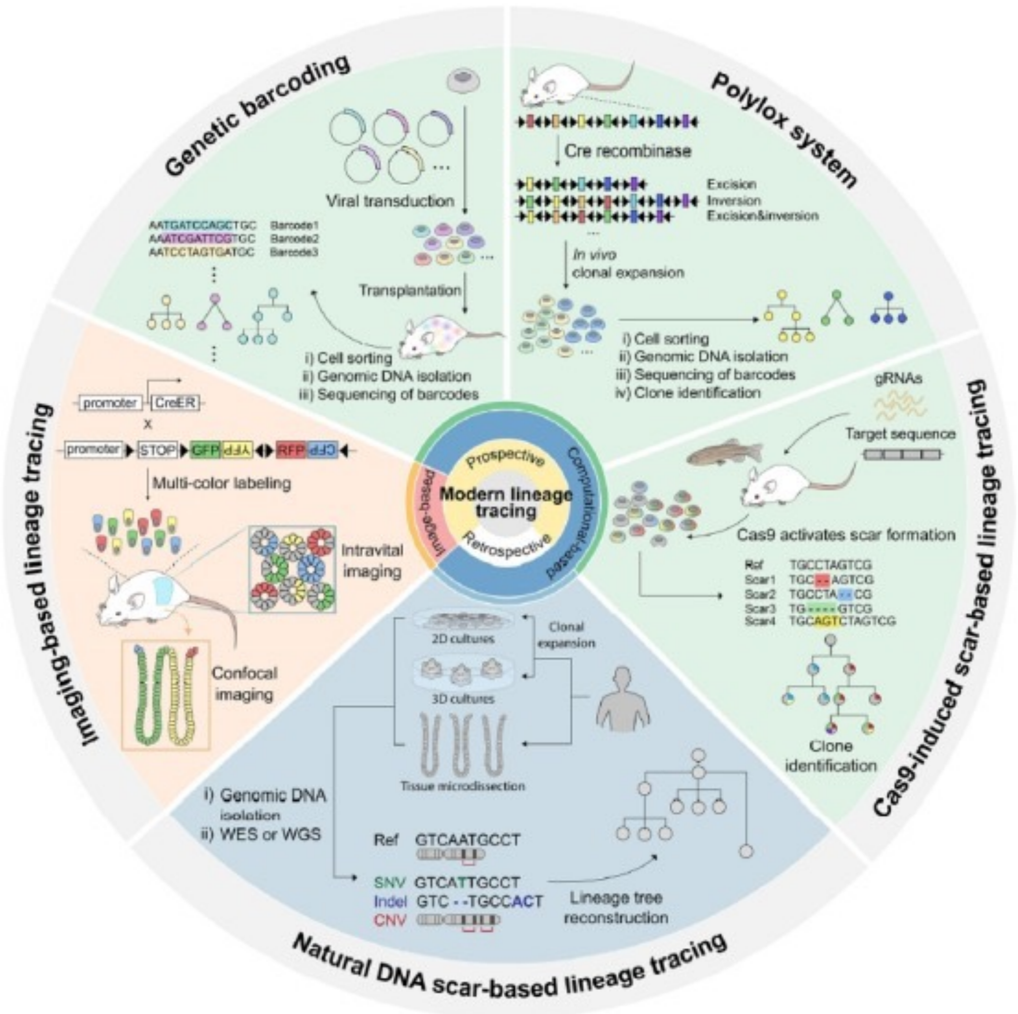


PVRI (Pulmonary Varscular Research Institute)

Lineage tracing

“set of methods that allow us to follow the fate of individual cells and their progeny with minimal disturbance of their physiological function”





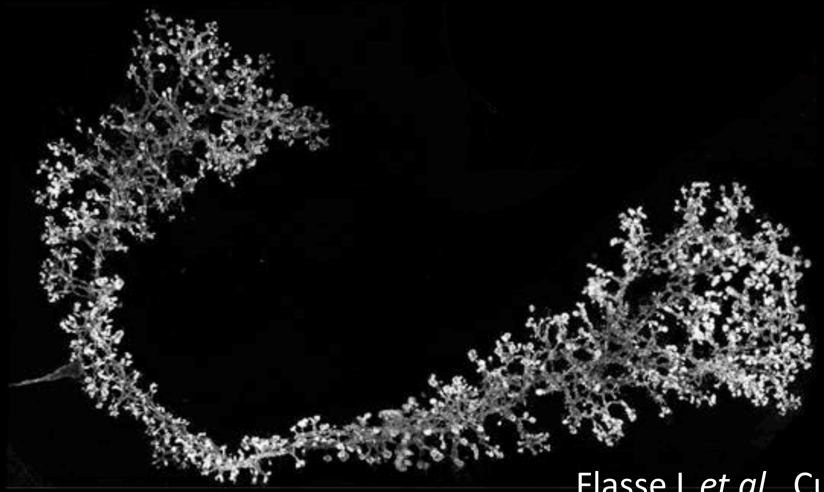
Wu et al., Mol Cells. 2019 Feb 28; 42(2): 104–112

Branching morphogenesis shapes a variety of epithelial organs

Kidney

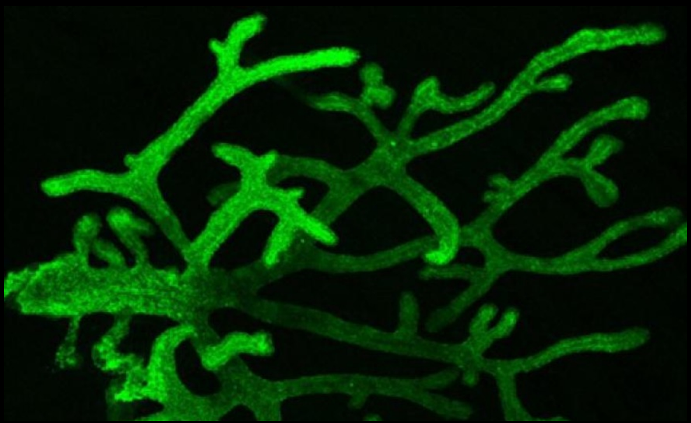
Short *et al.*, *Elife* 2018

Pancreas



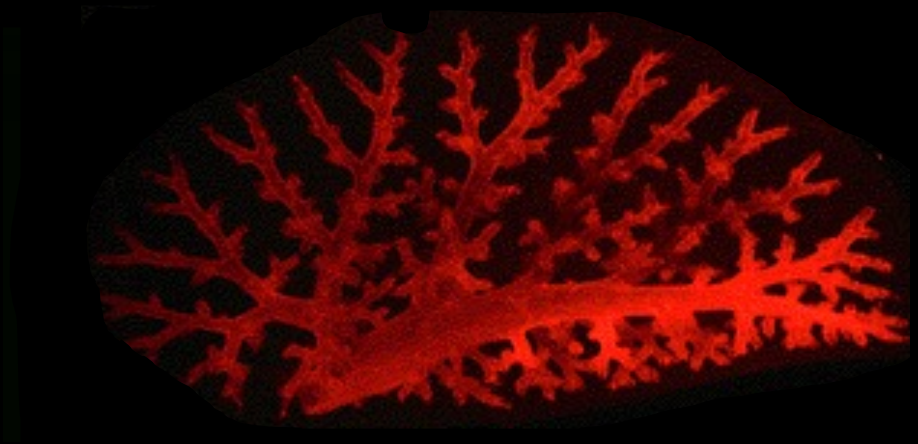
Flasse L *et al*., Curr *Top Dev Biol.* 2021

Mammary gland



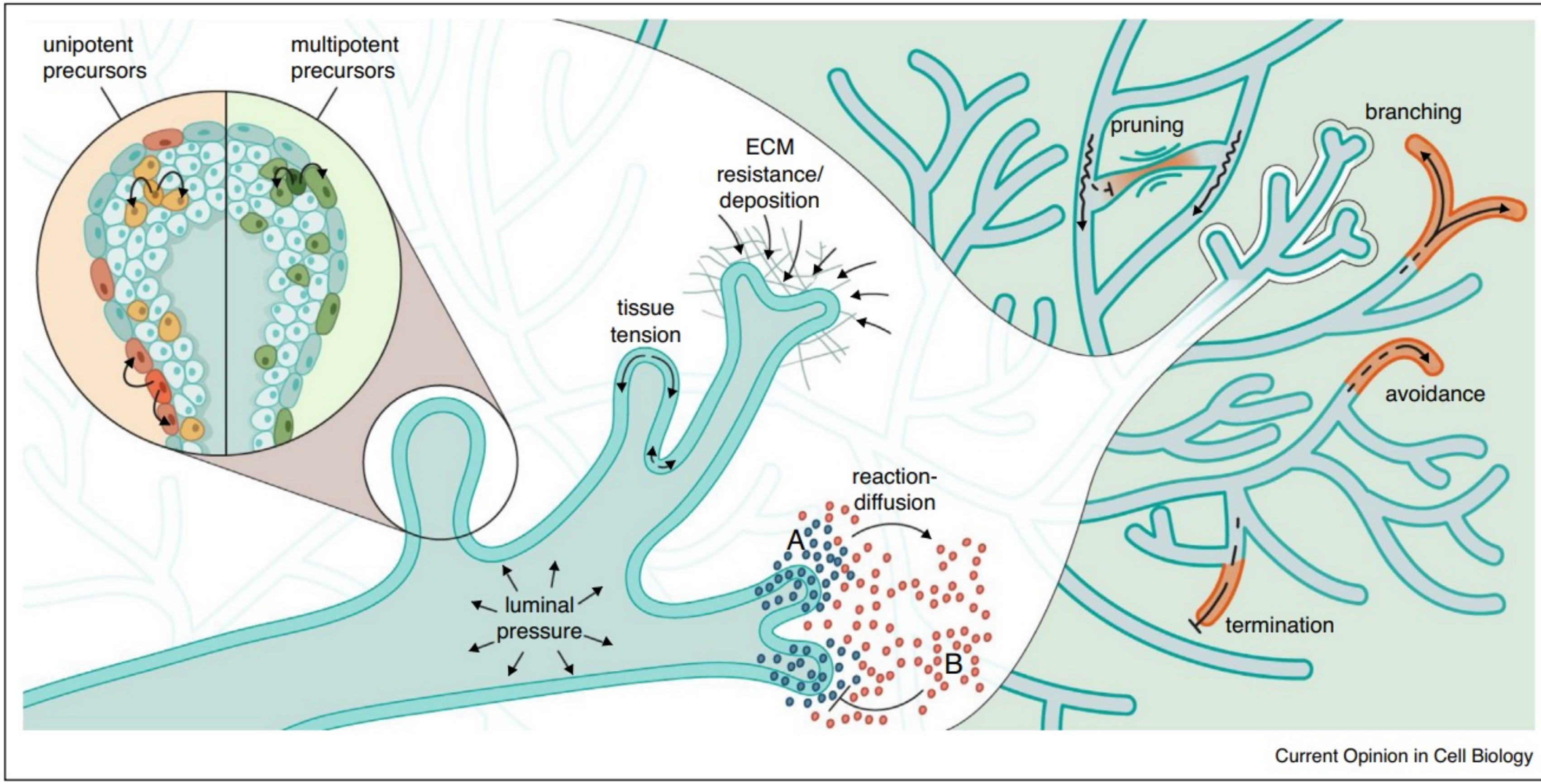
Olivia Harris, University of Cambridge, Wellcome Images

Lung



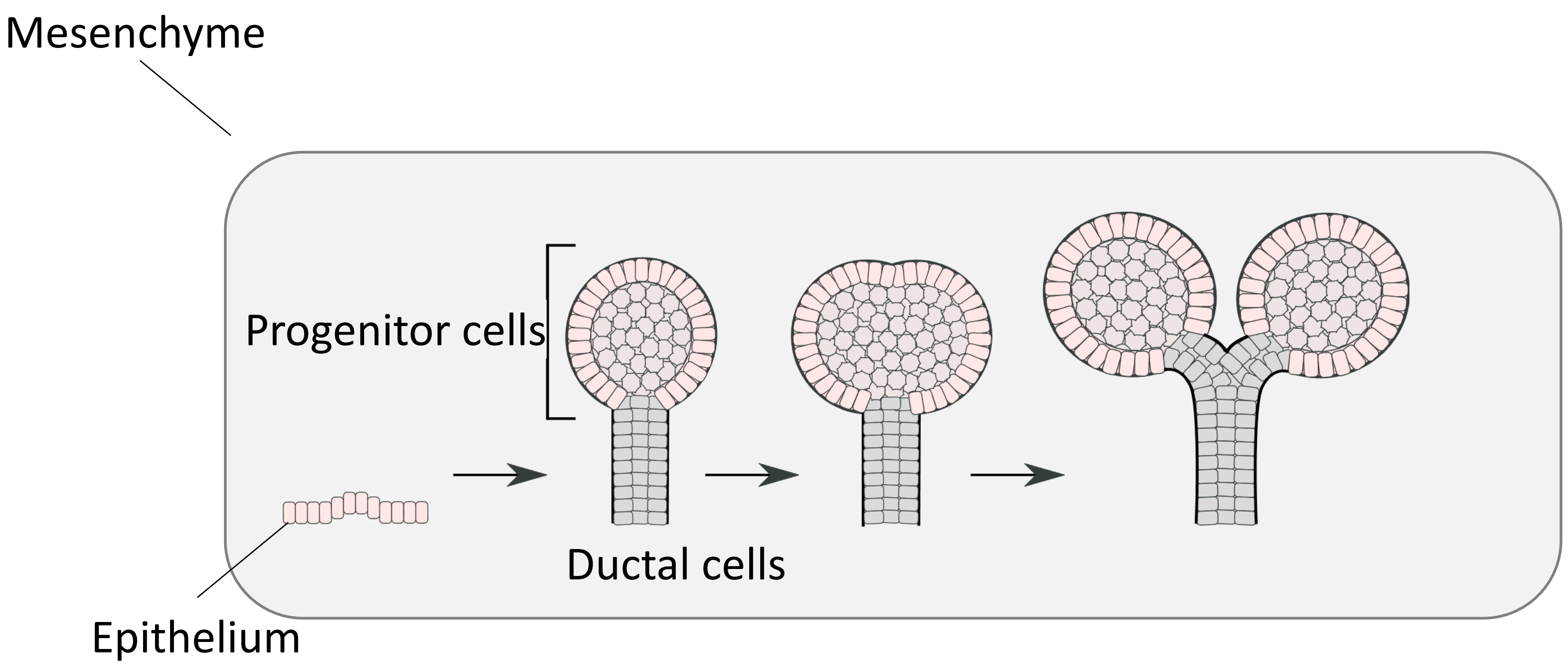
thoracickey.com

Multi-scale dynamic of branching morphogenesis

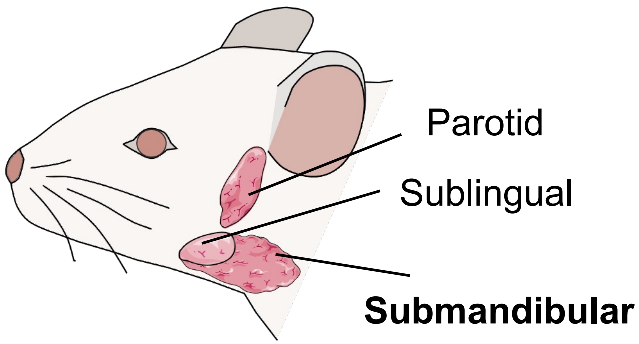


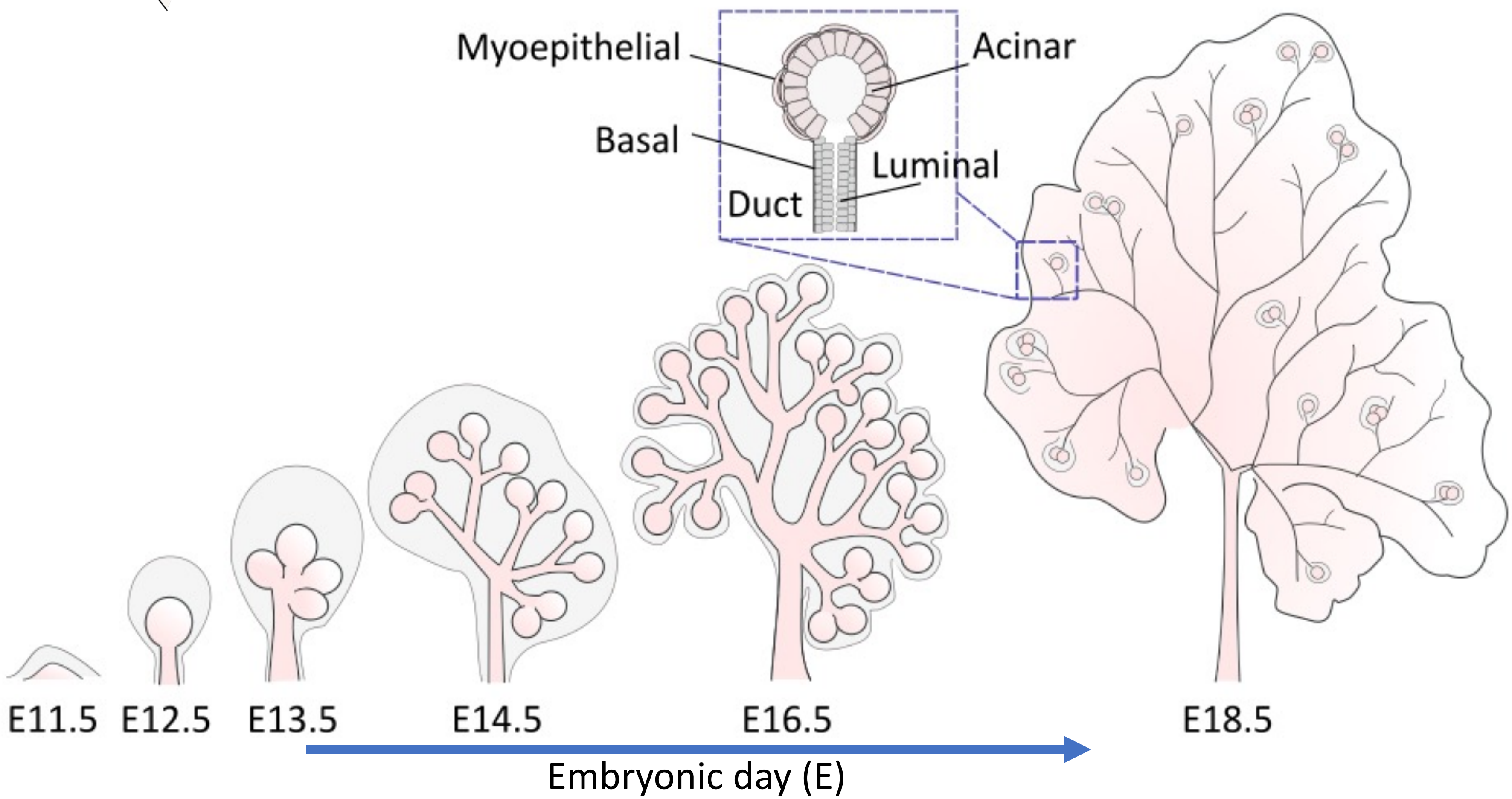
Hannezo and Simons, Curr. Opin. Cell Biol. (2019)

Epithelial patterning through branching morphogenesis

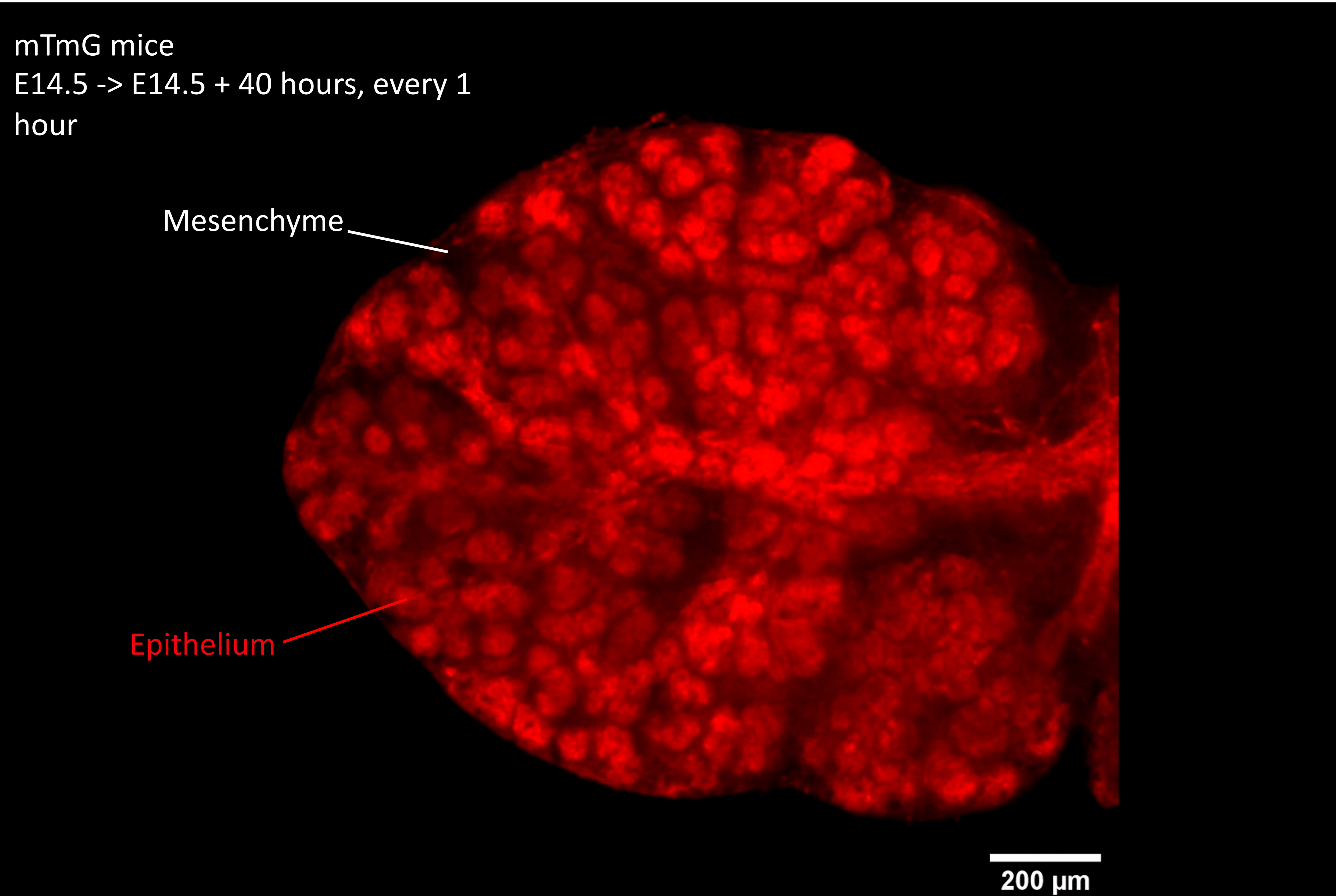


Epithelial patterning through branching morphogenesis

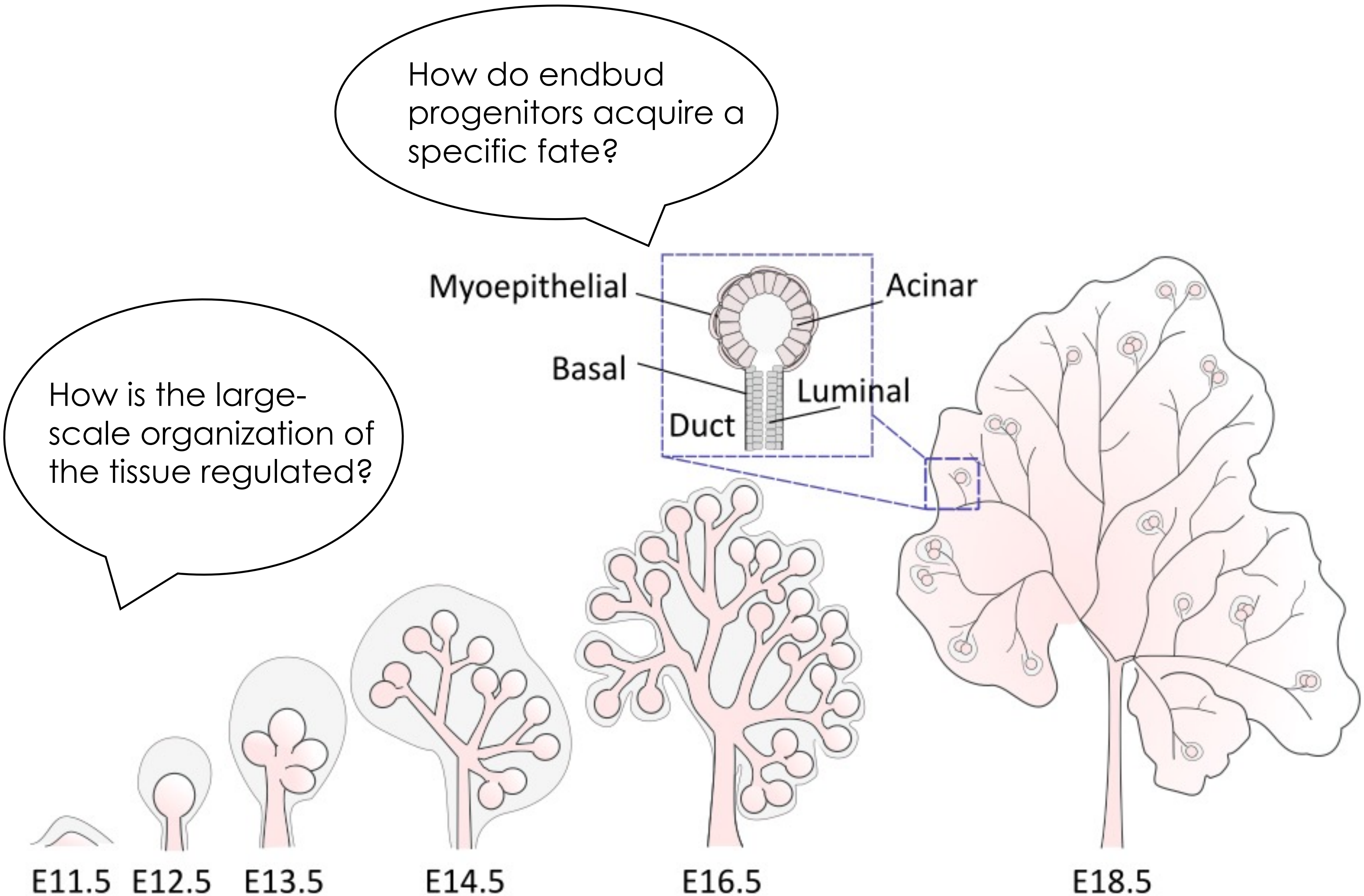




Salivary gland explant

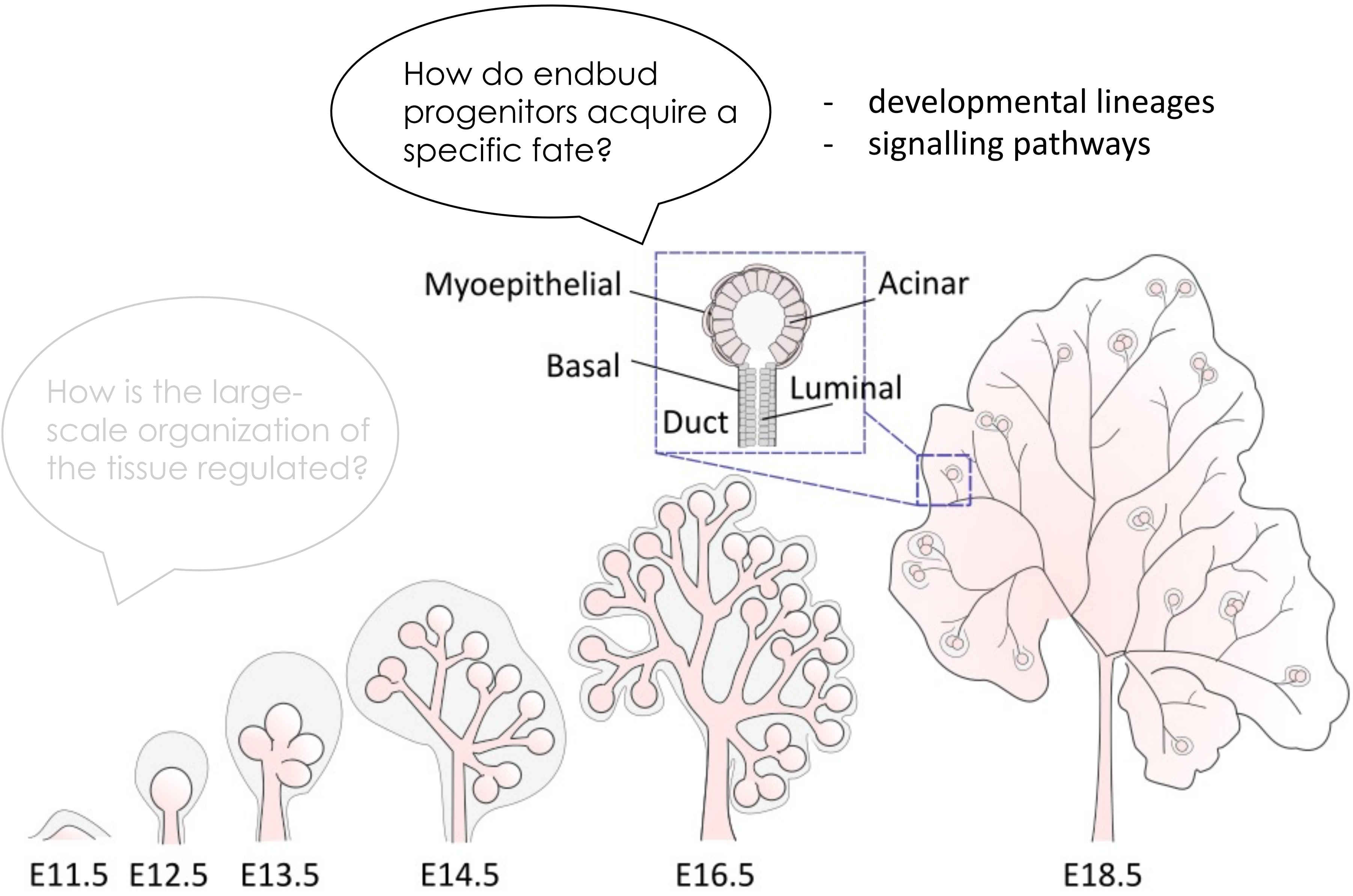


Defining branching morphogenesis from the cellular to the large scale

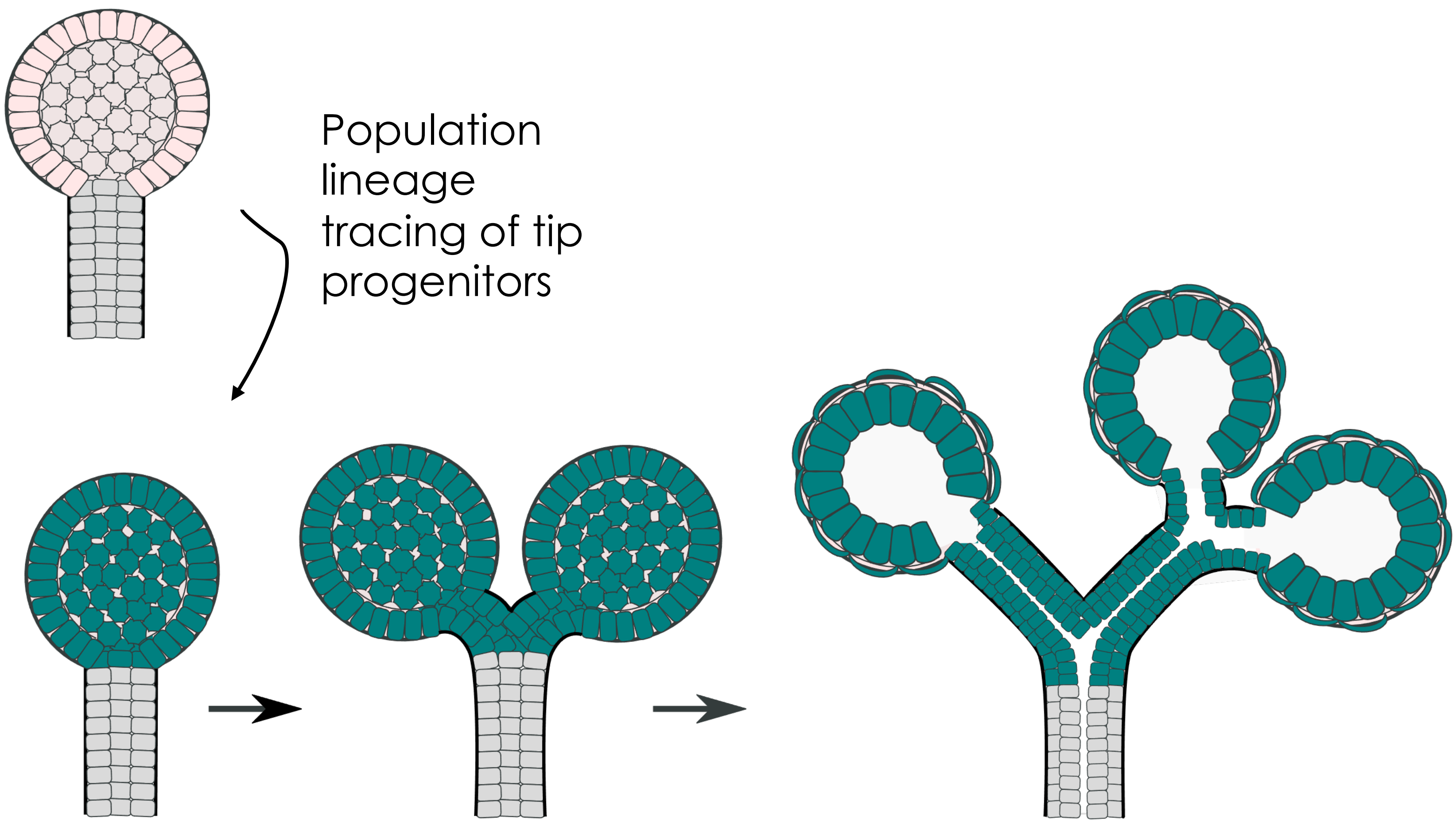


Branching morphogenesis from the cellular to the large scale

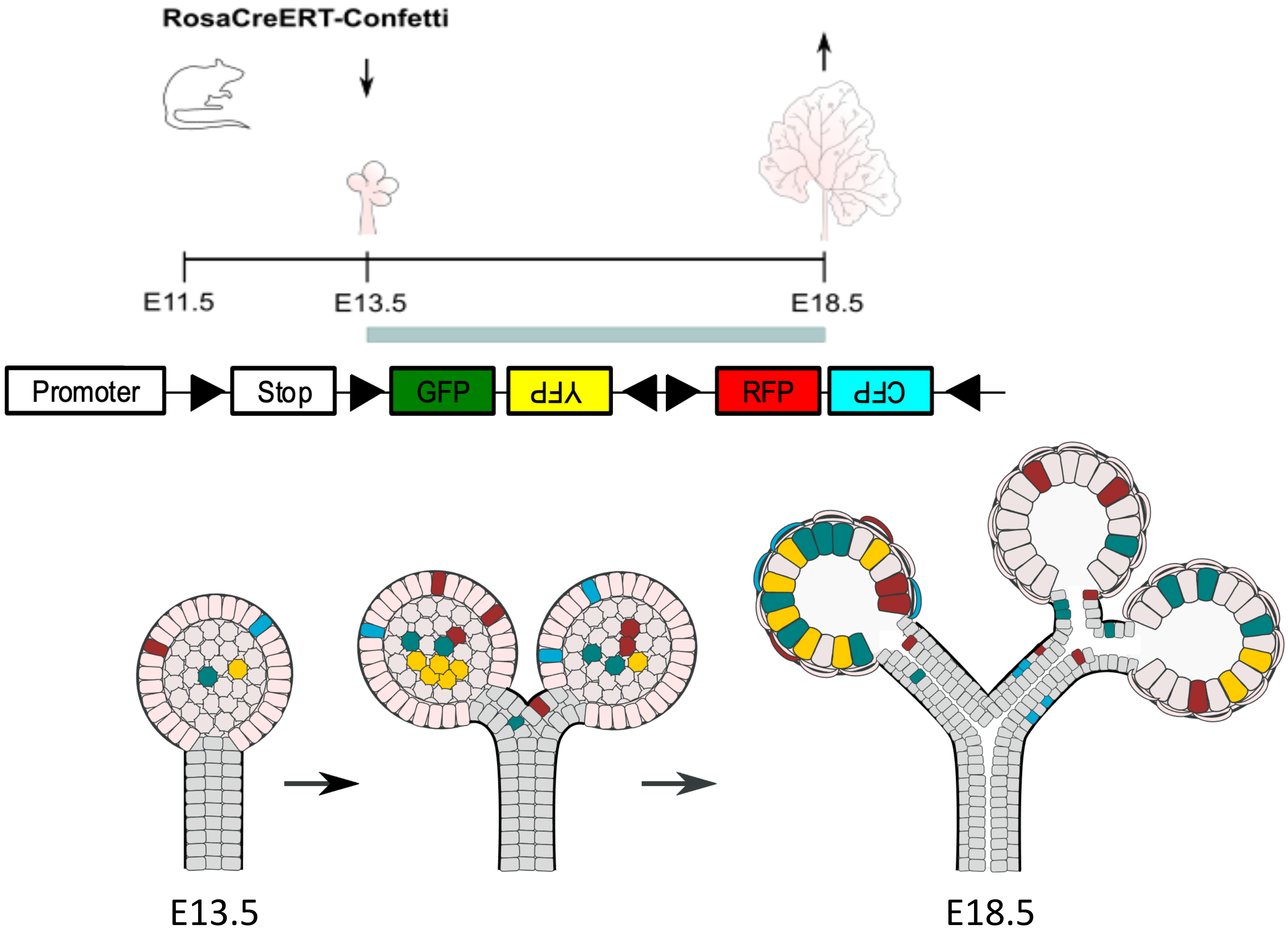
- developmental lineages
- signalling pathways



How do endbud progenitors acquire a specific fate?



Unbiased lineage tracing with *RosaCreERT;Confetti*



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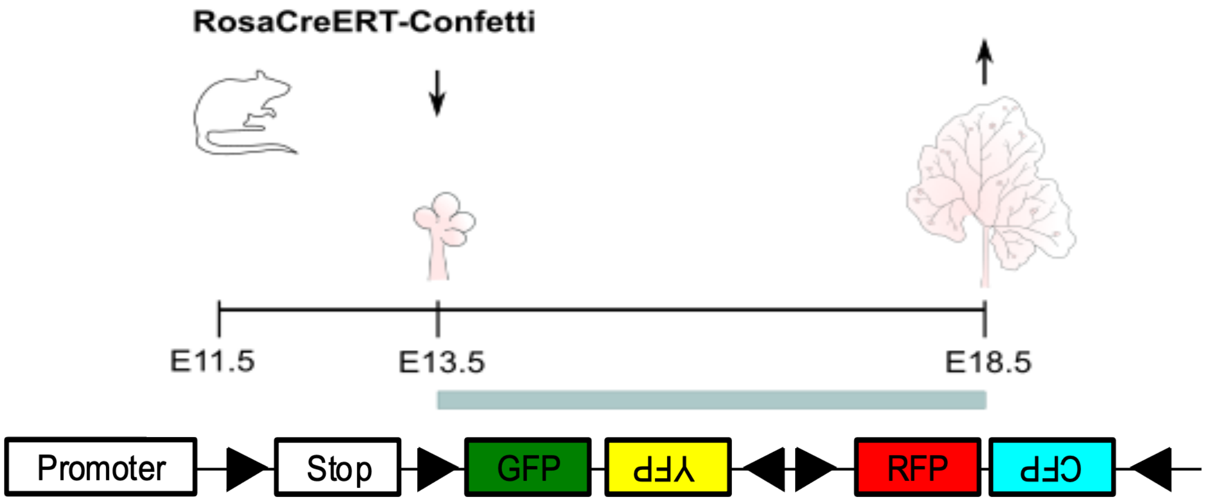
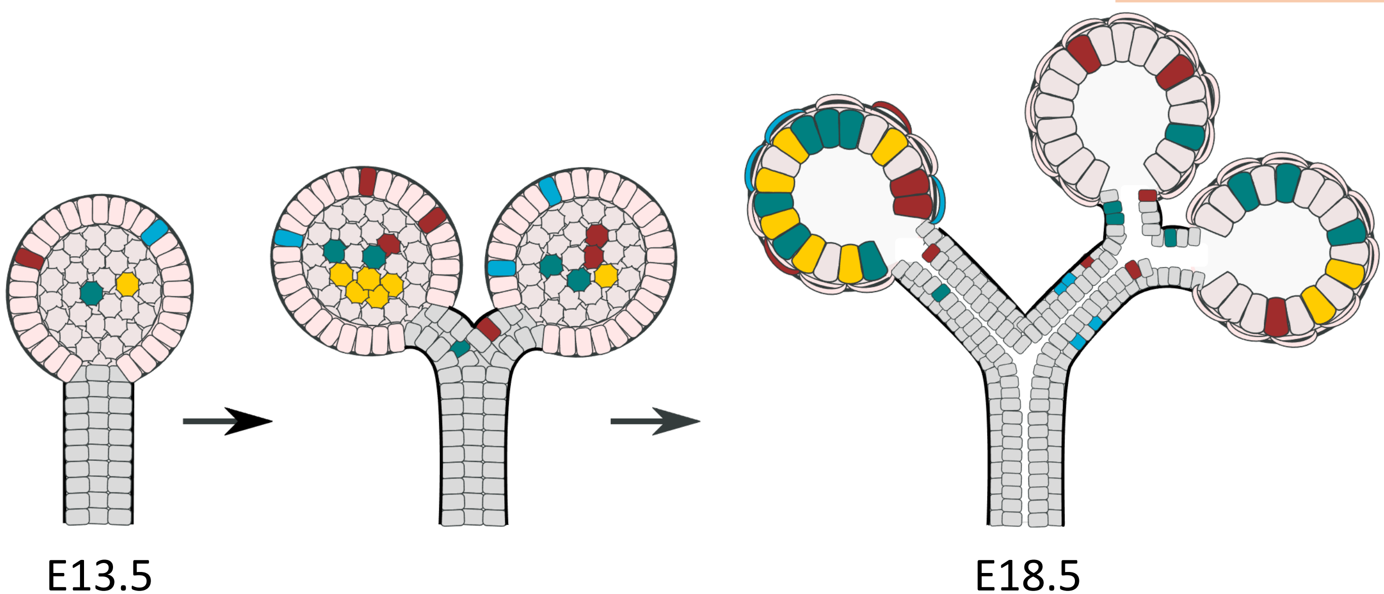


<u>RFP population</u>
1x Myoepithelial
5x Acinar
2x Basal ductal
2x Luminal ductal



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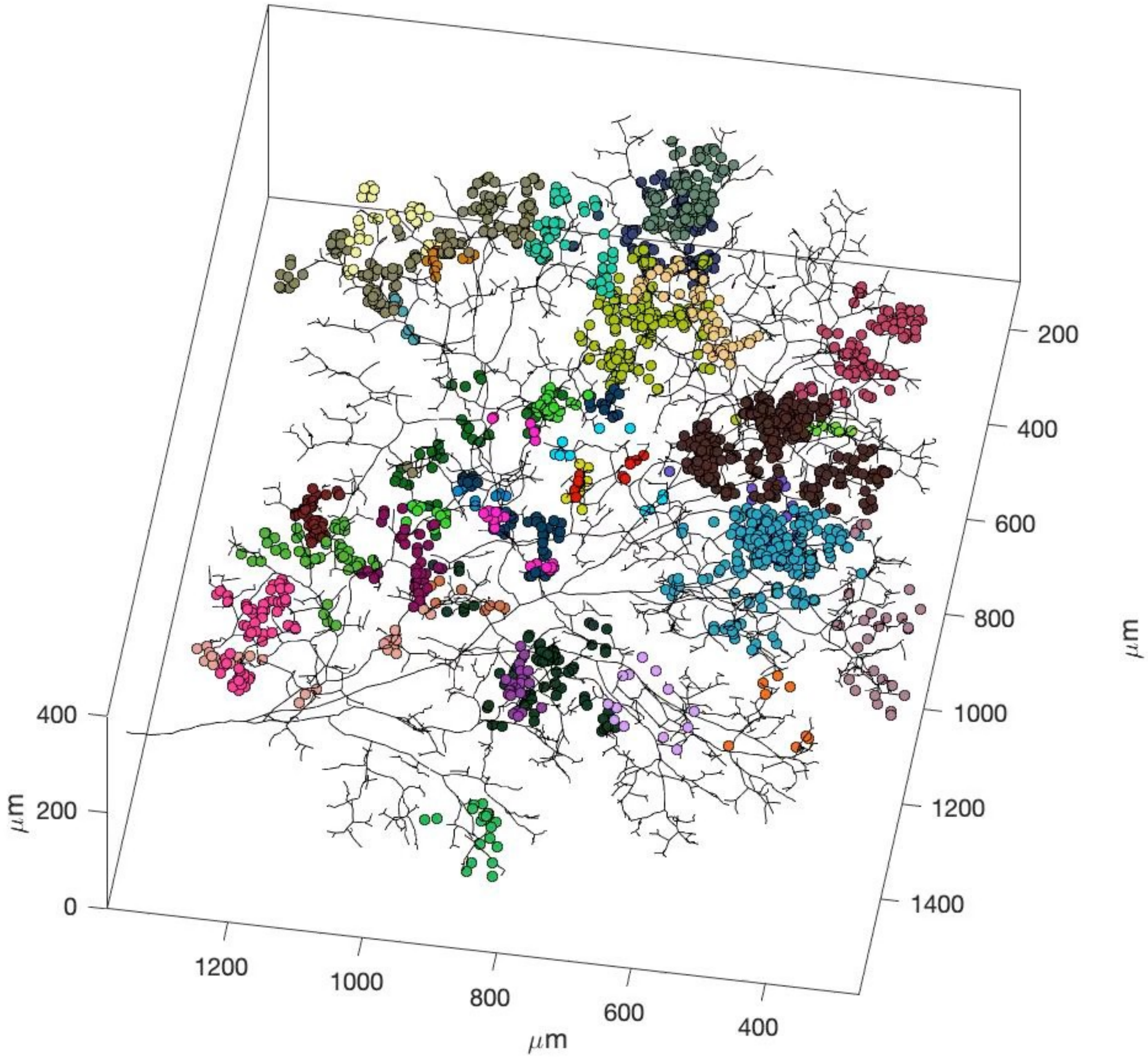

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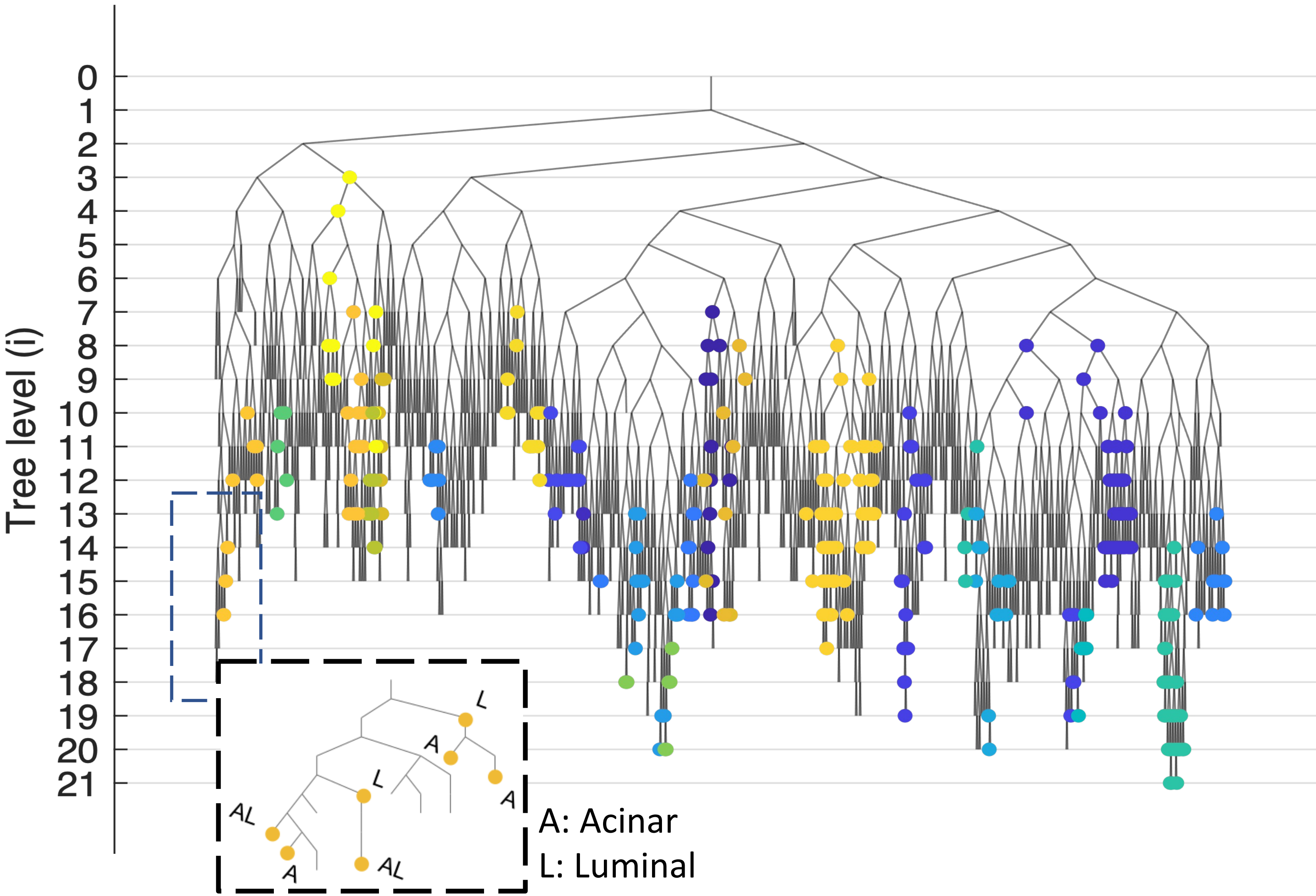
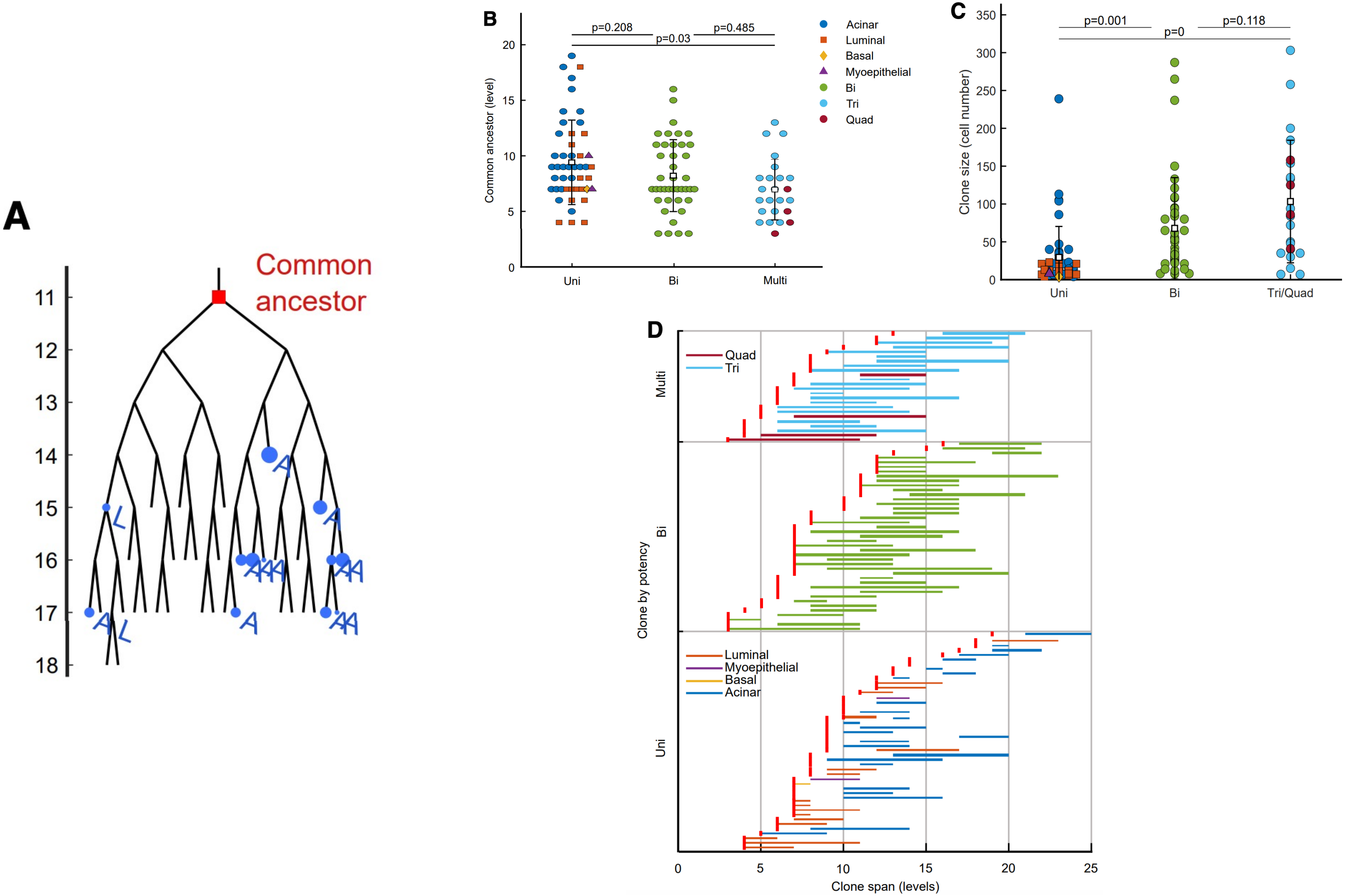
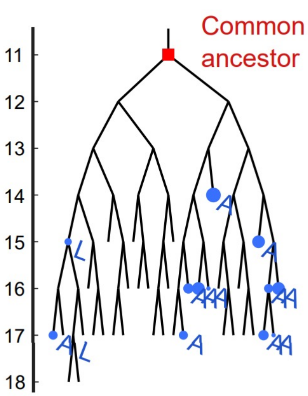


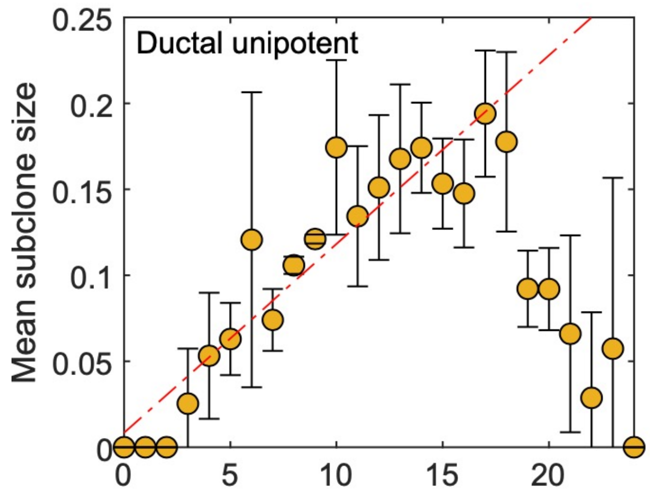
Potency decreases with branching



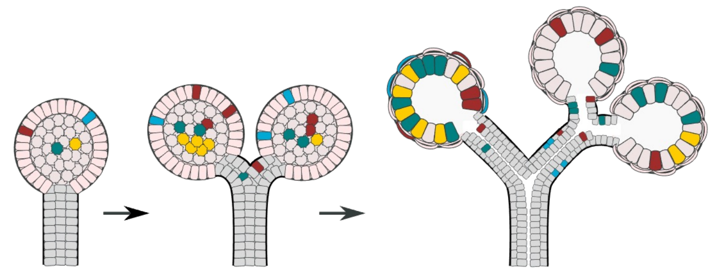
From modeling: Endbud are well-mixed

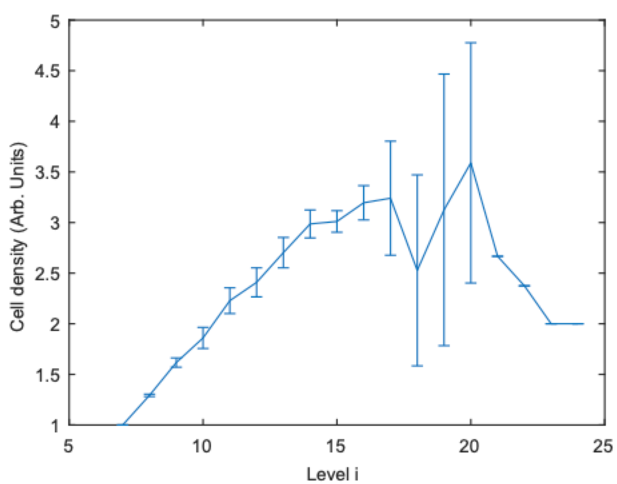
A



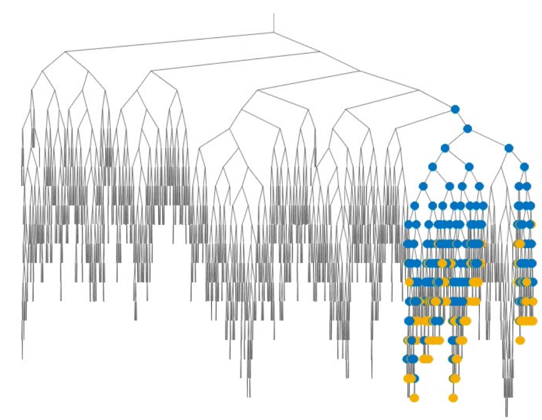


Linear increase in subclone size with the level i nthe tree





Random choice model

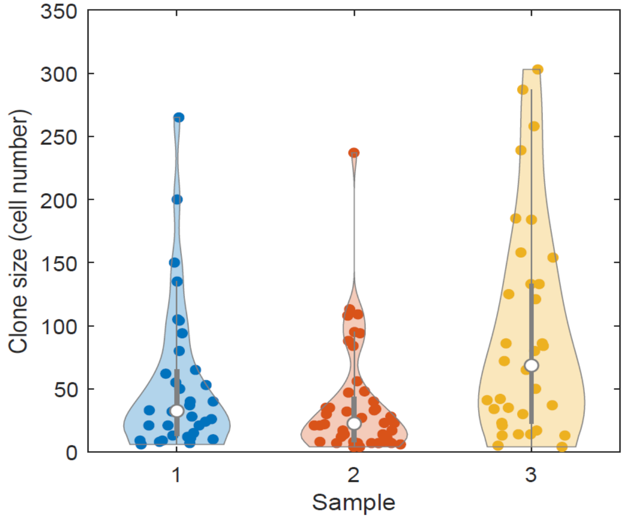


Simple model suggests a well-mixed (fluid-like) behaviour of cells in endbuds

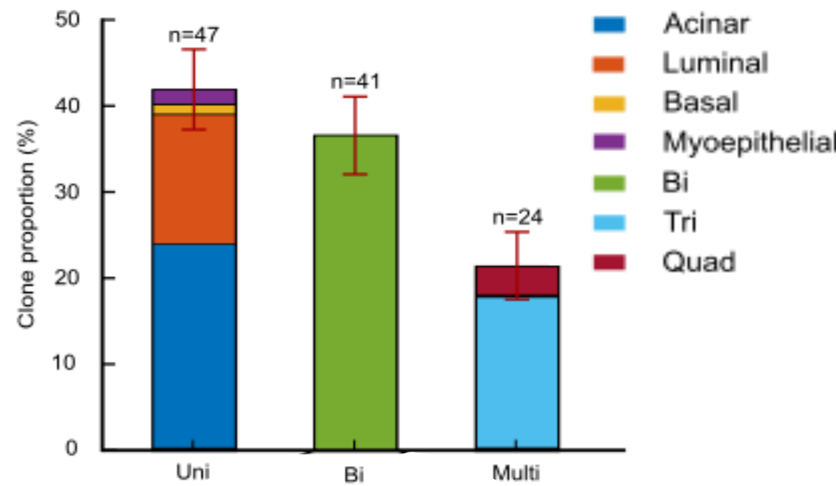
Endbud progenitors are heterogeneous

Tracing
E13.5→ E18.5
RosaCreER;
Confetti

Heterogeneity in clone size

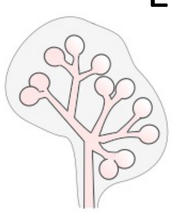


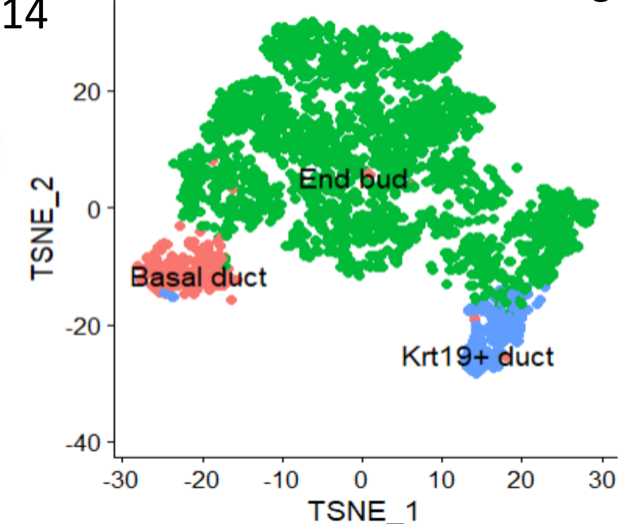
Heterogeneity in potency

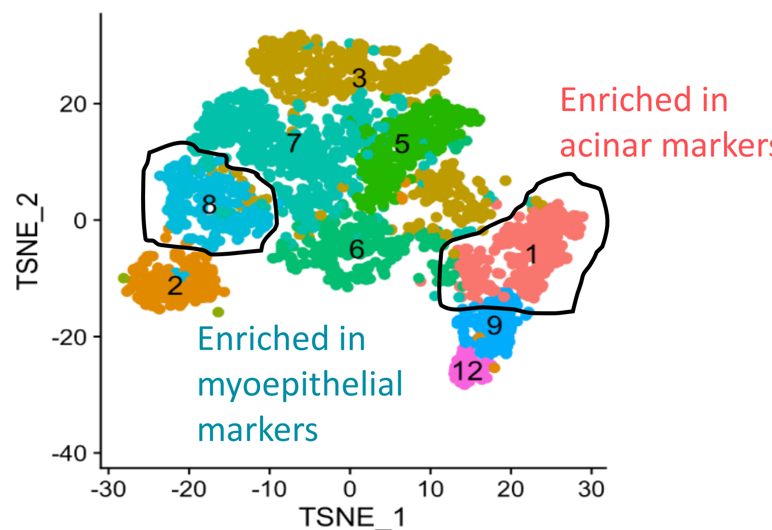


Heterogeneity at the transcriptional level

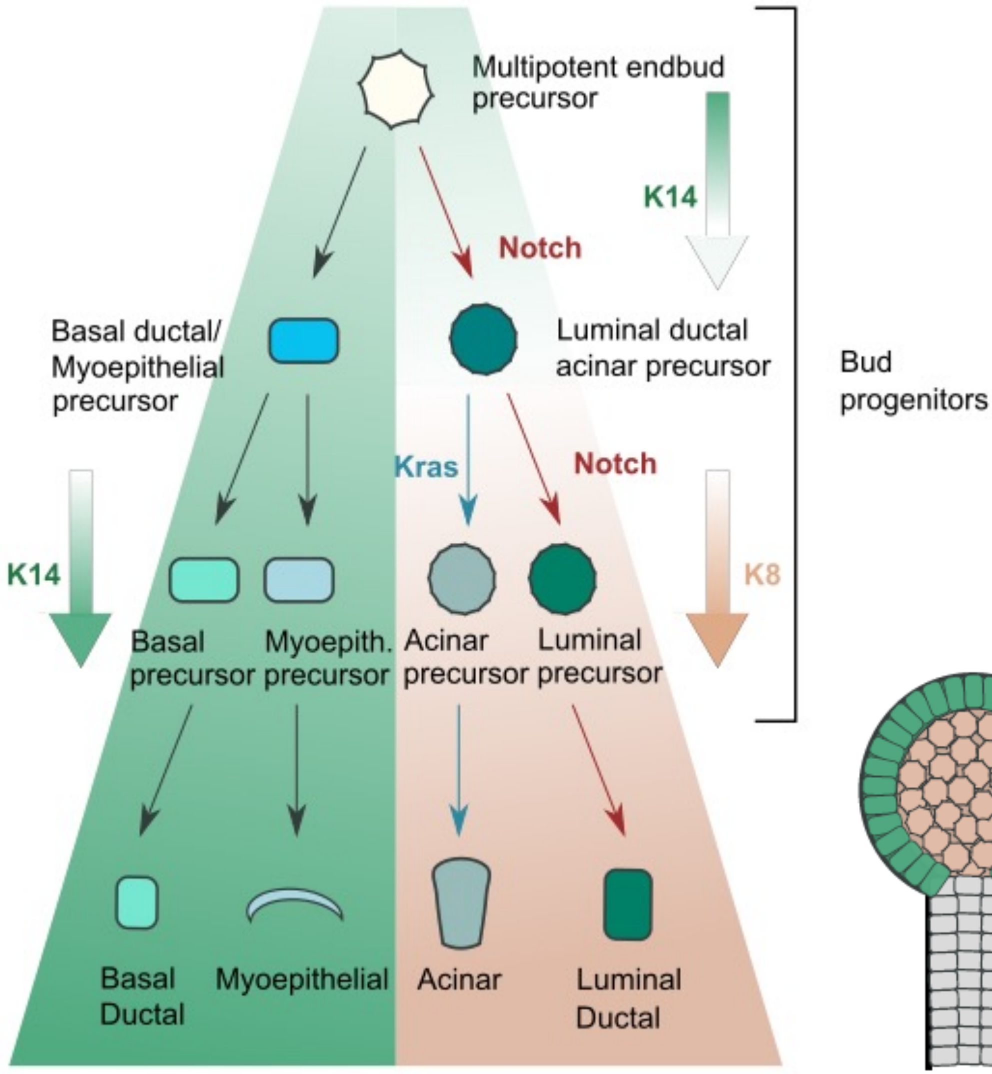
E14

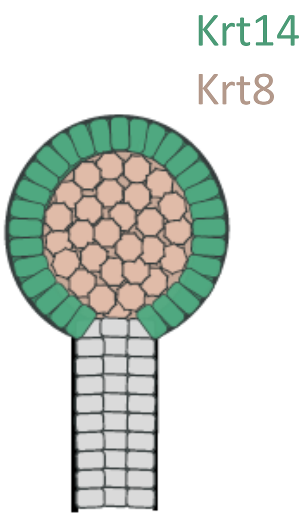


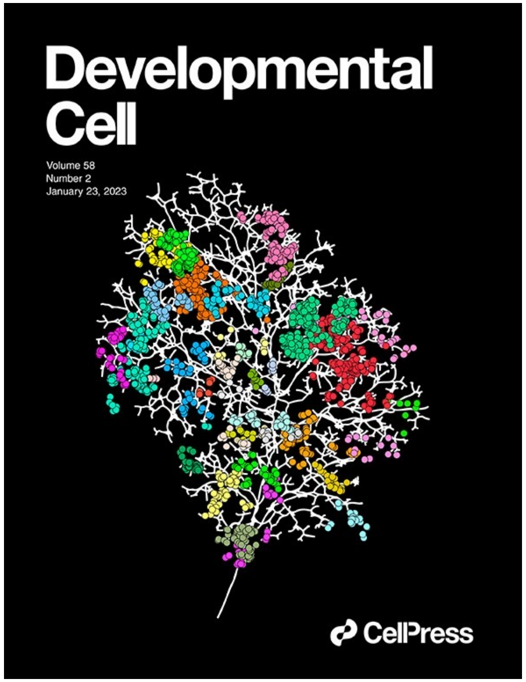




The hierarchical organization of endbud progenitors in salivary glands







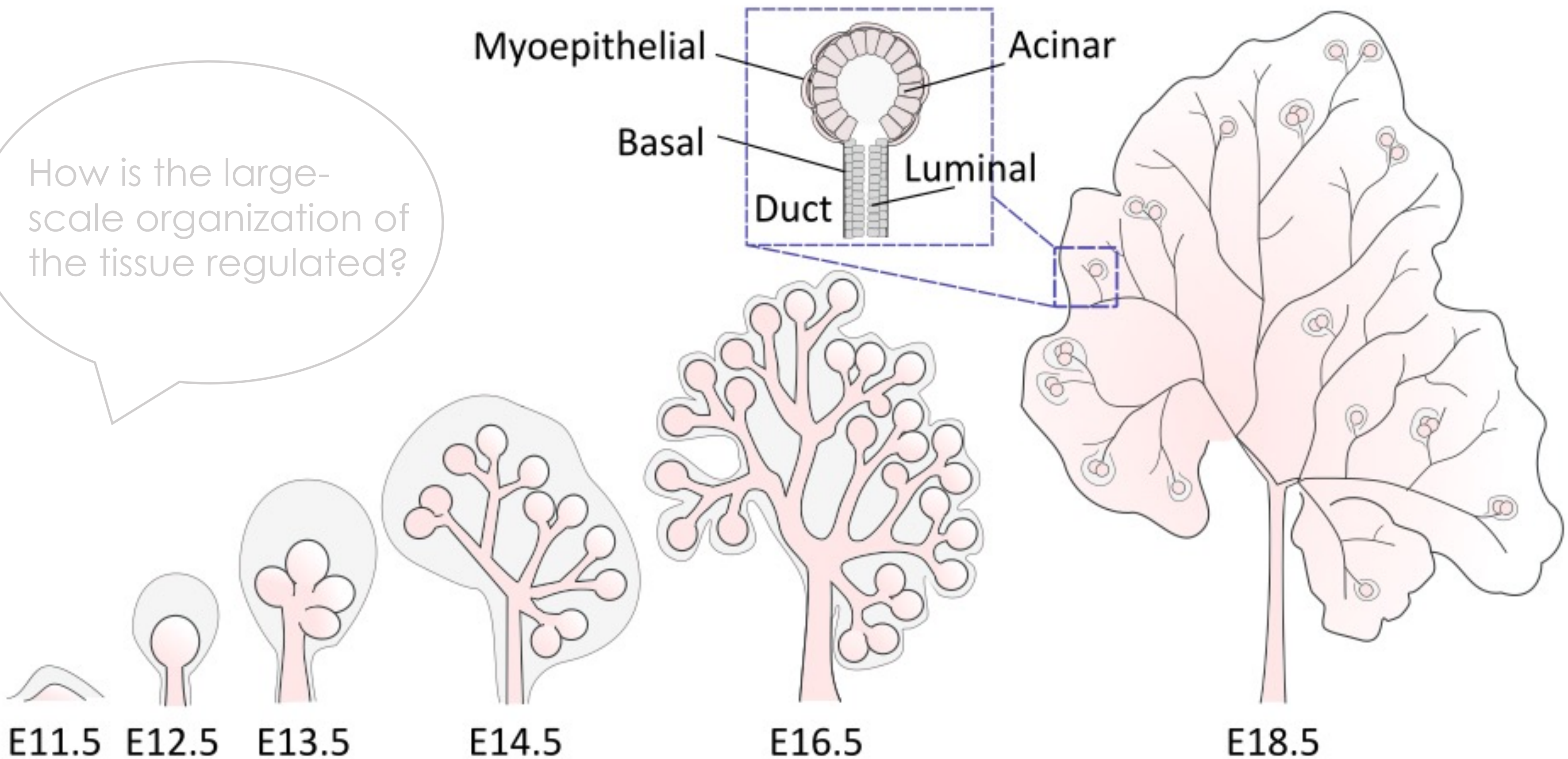
Chatzeli L*, Bordeu I* *et al., Dev. Cell*. 2023

Branching morphogenesis from the cellular to the large scale

How do endbud progenitors acquire a specific fate?

- Heterogeneous endbud progenitors
- Hierarchical model of lineage restriction
- Notch promotes specification of multipotent progenitors and the luminal fate
- Kras promotes the acinar fate

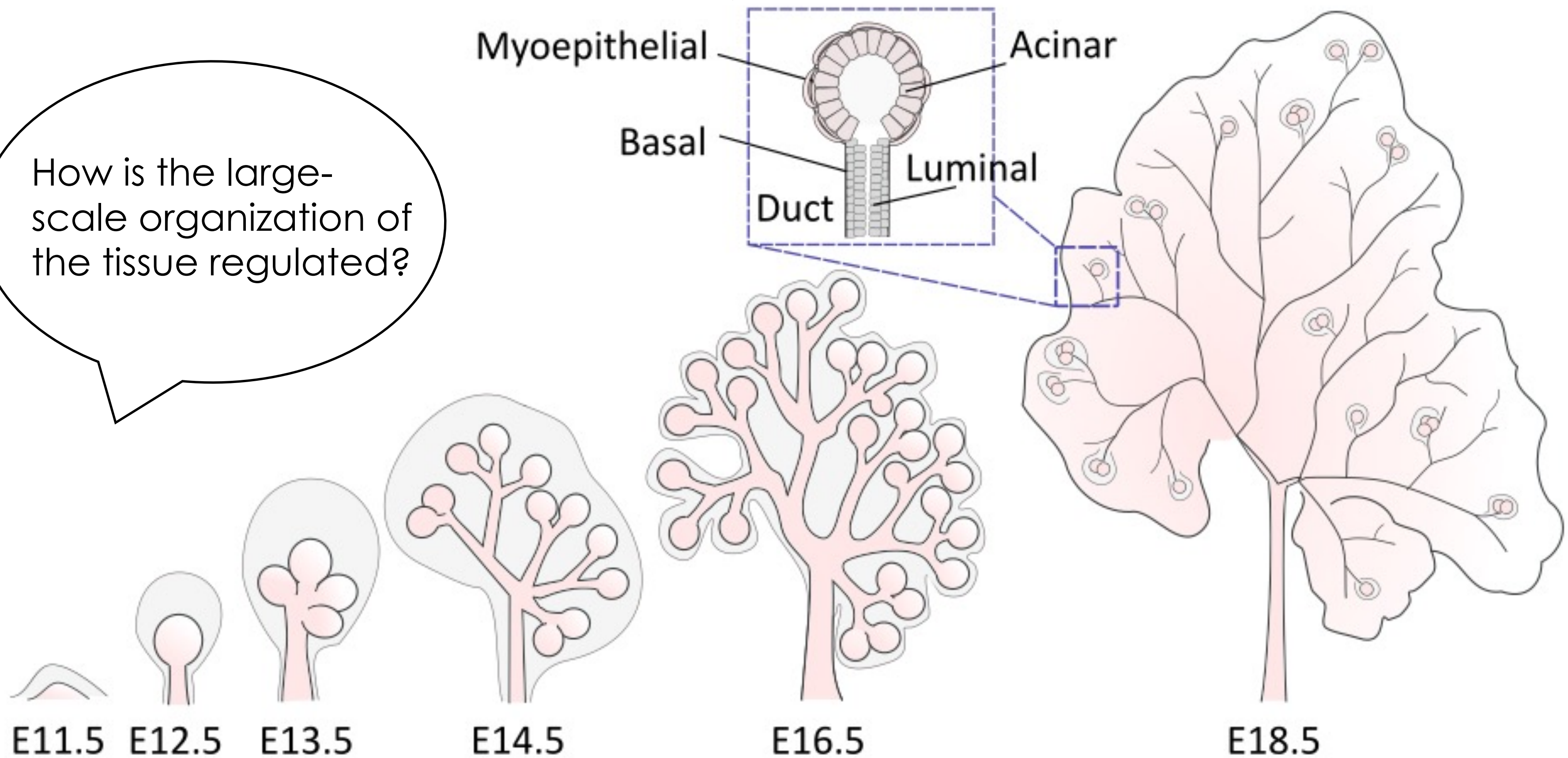
How is the large-scale organization of the tissue regulated?



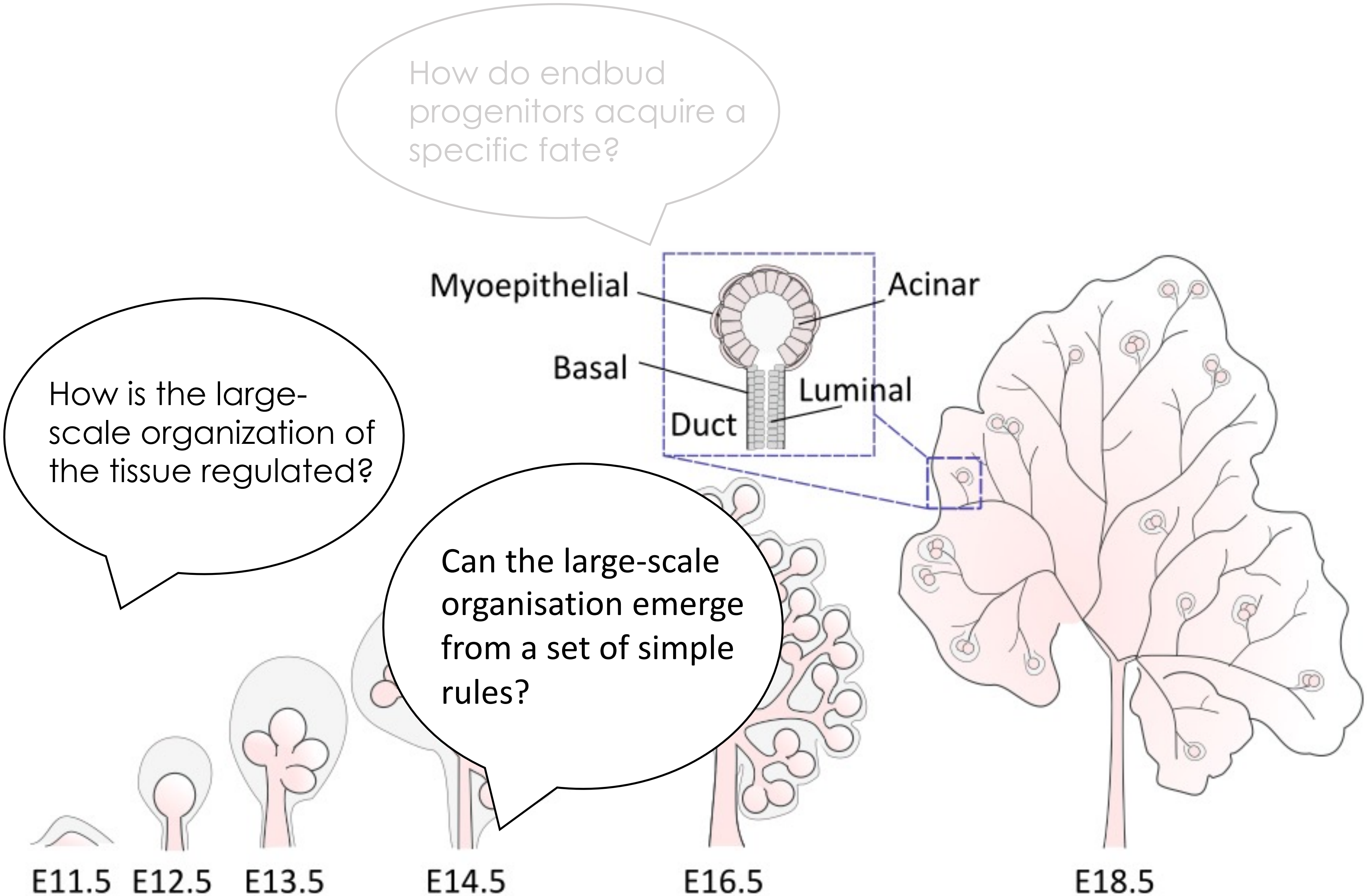
Branching morphogenesis from the cellular to the large scale

How do endbud progenitors acquire a specific fate?

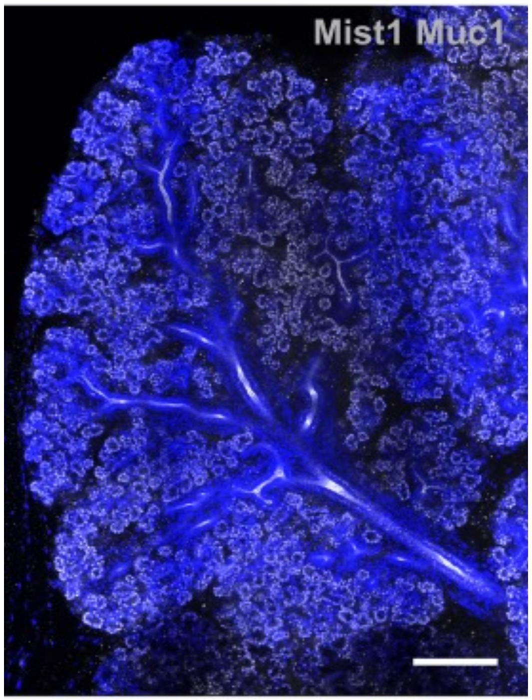
How is the large-scale organization of the tissue regulated?

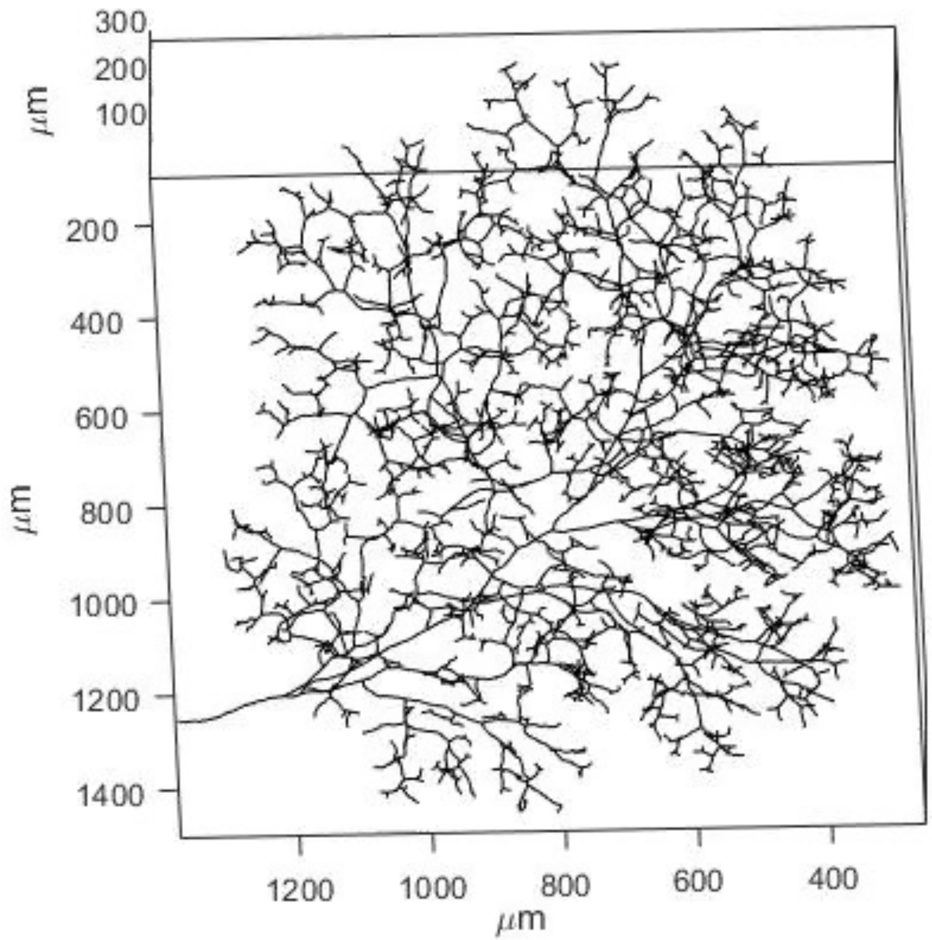


Branching morphogenesis from the cellular to the large scale



Segmentation of the salivary gland 3D ductal network

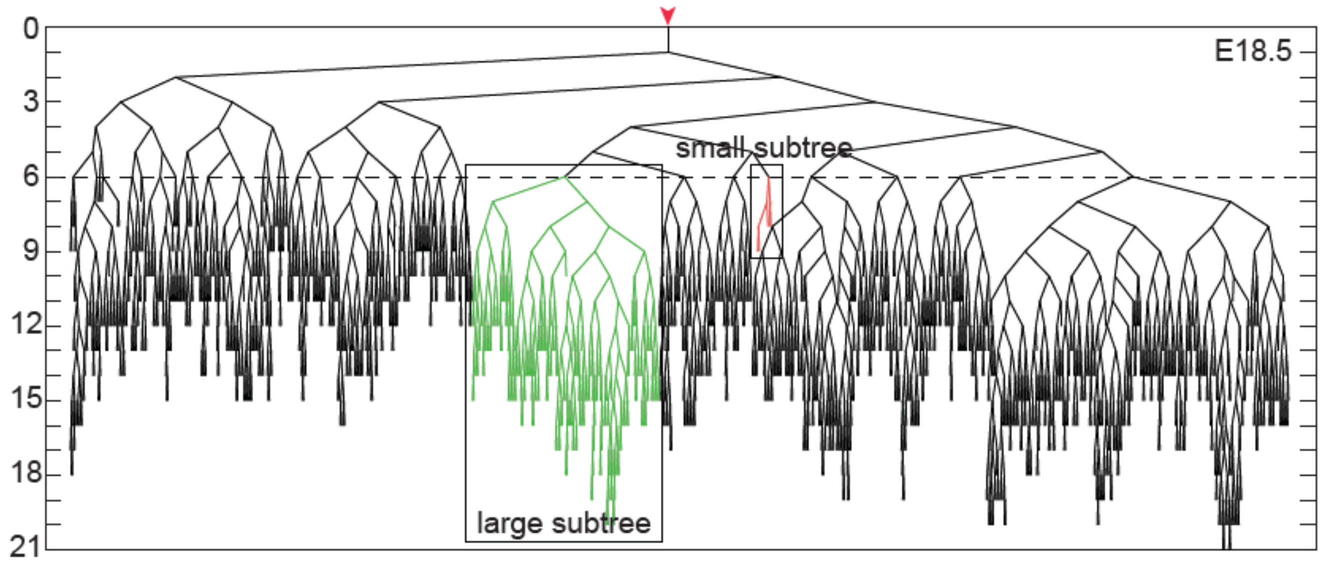


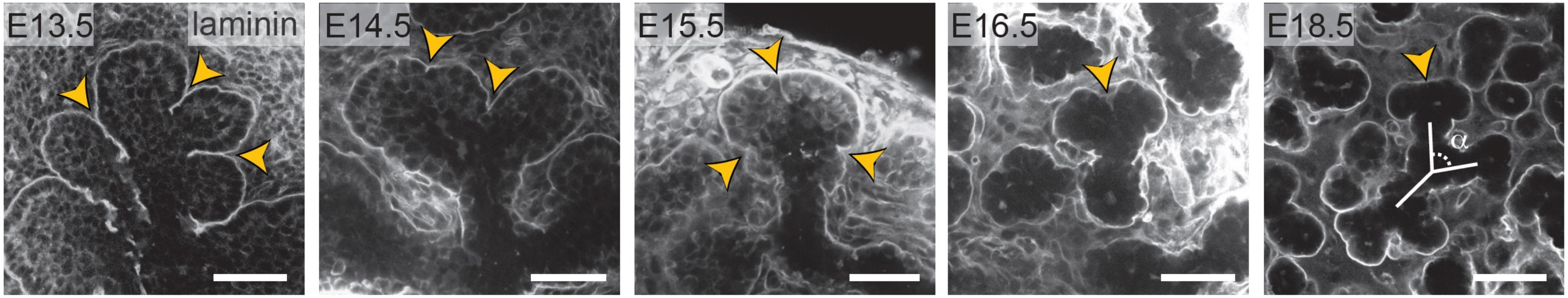


Salivary gland exhibits two distinct phases of growth

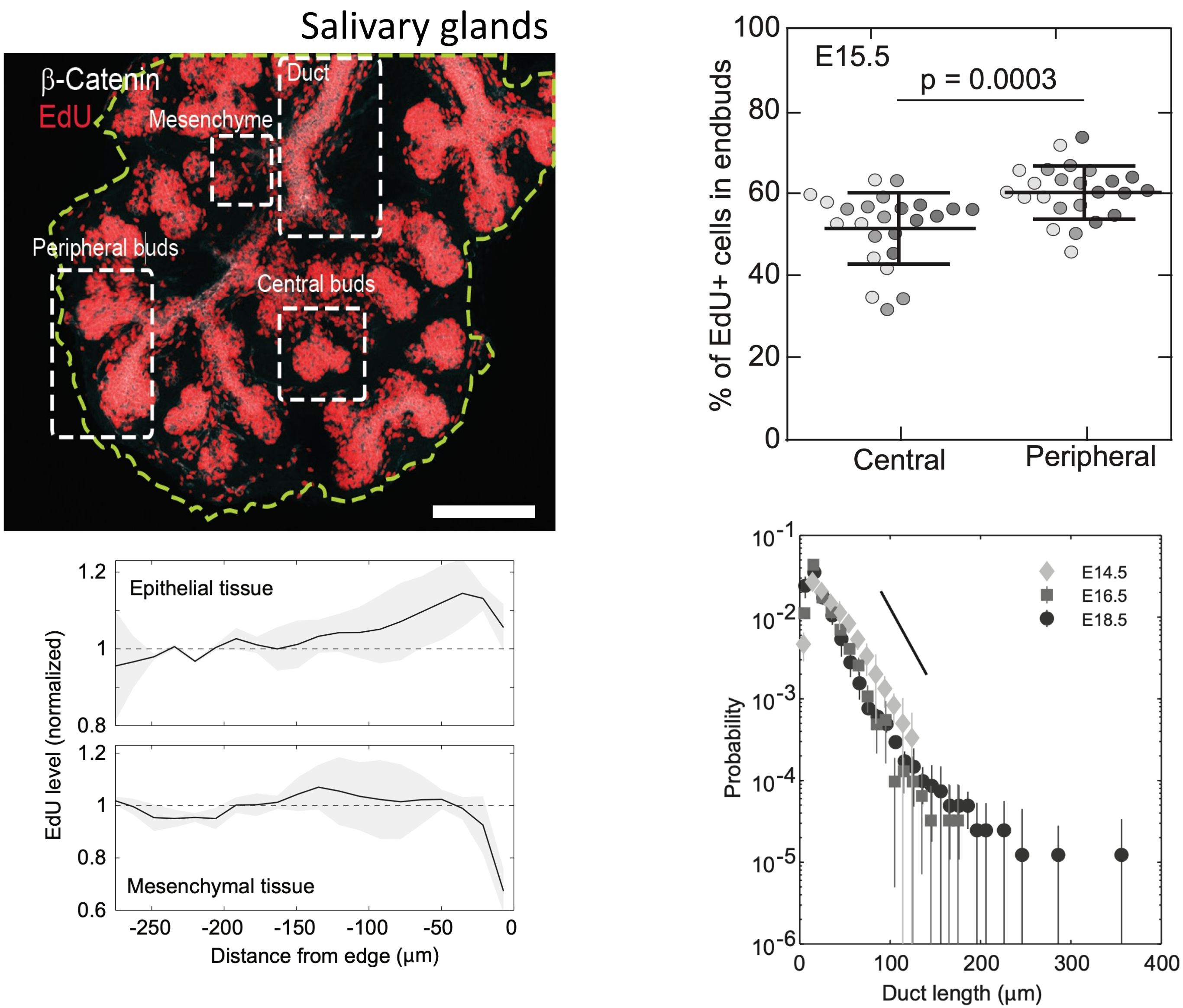
Early stage
Stereotypic rudimentary tree

Late stage
Non-stereotypic



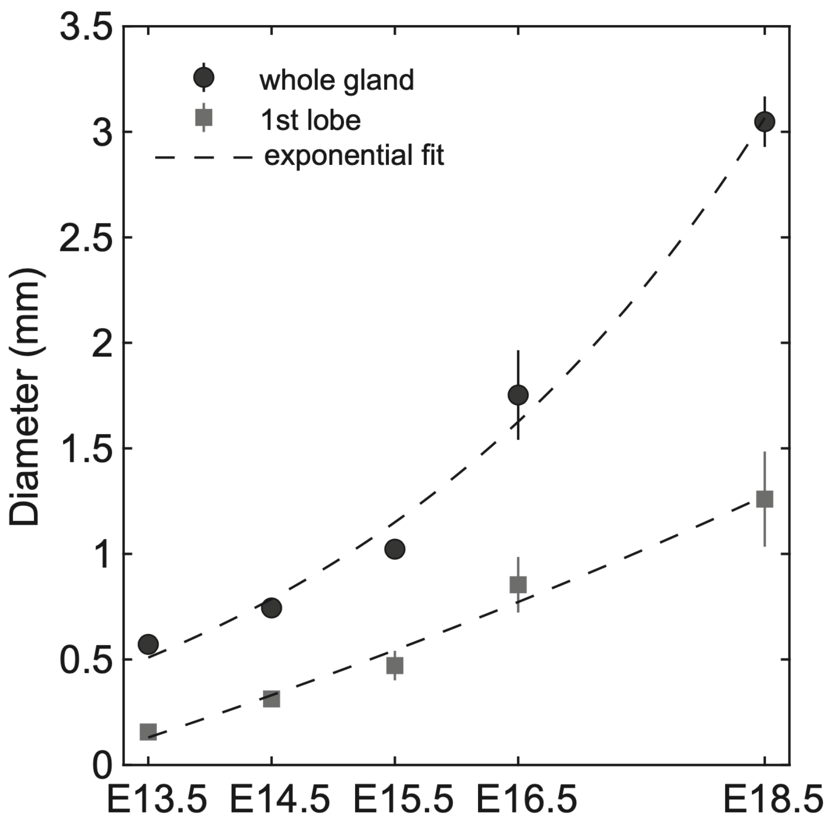


Salivary gland exhibits a distinct patterns of proliferation



Submerged tips, duct and mesenchyme continue proliferating!

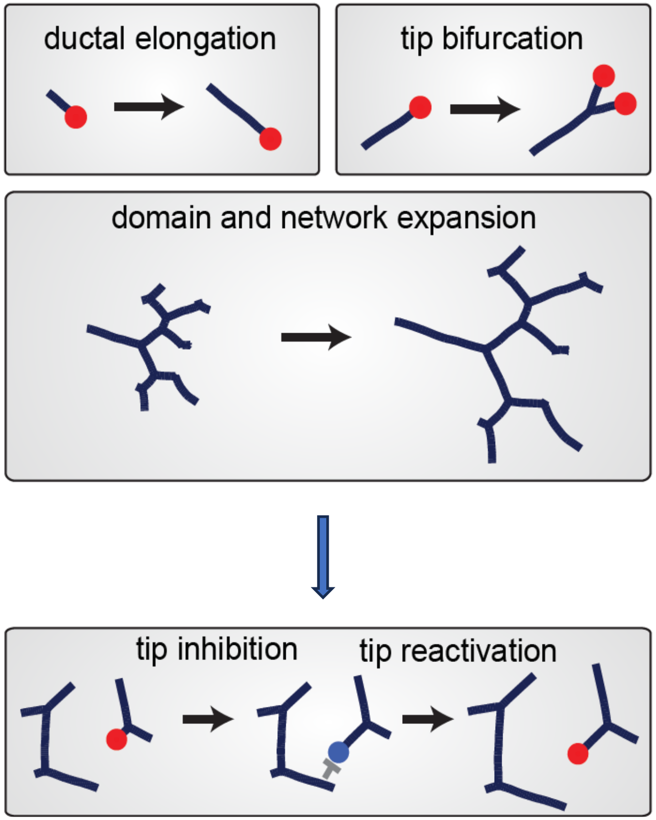
Salivary gland develops on an inflating domain



The gland inflates exponentially over time.

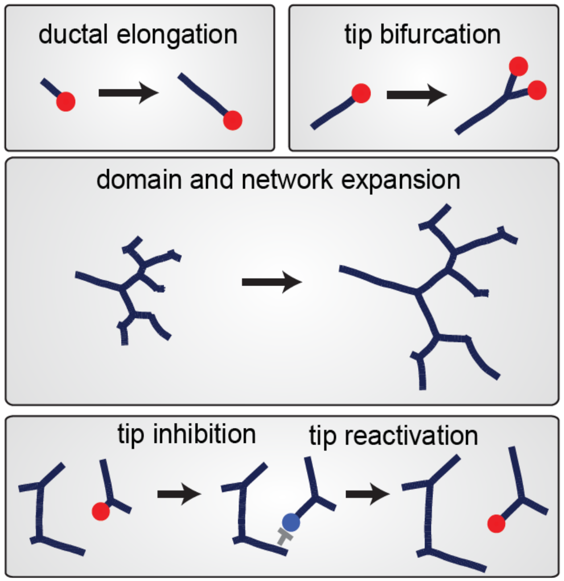
$$d = d_0 e^{R_{exp} t}$$

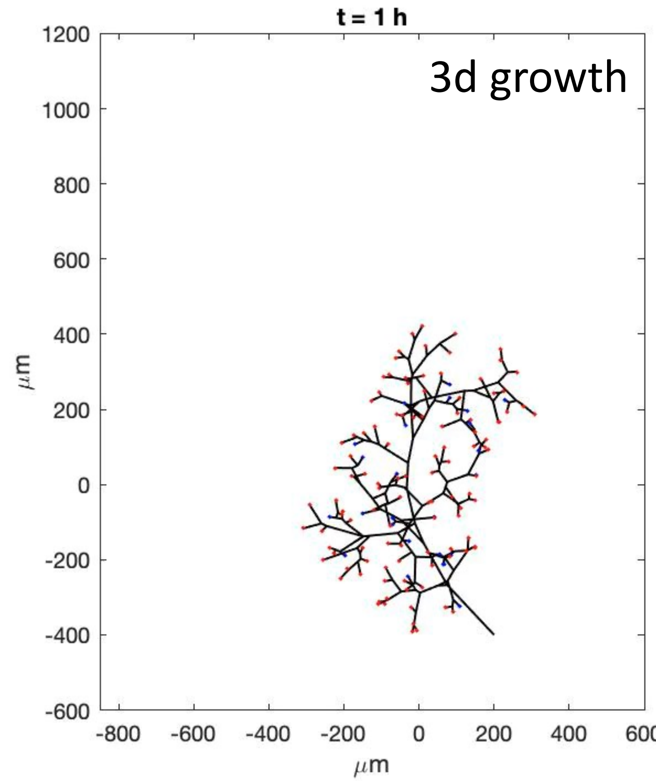
Branching morphogenesis is driven by tissue expansion

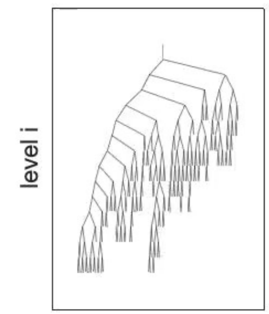


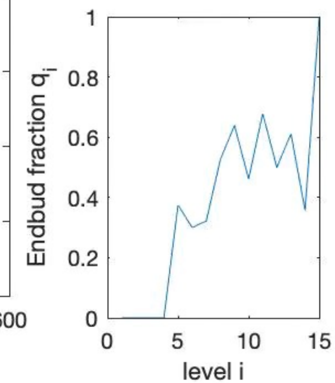
Inflationary **branching-*delayed*** random walk is driven by the permanente tissue expansion

Branching morphogenesis is driven by tissue inflation



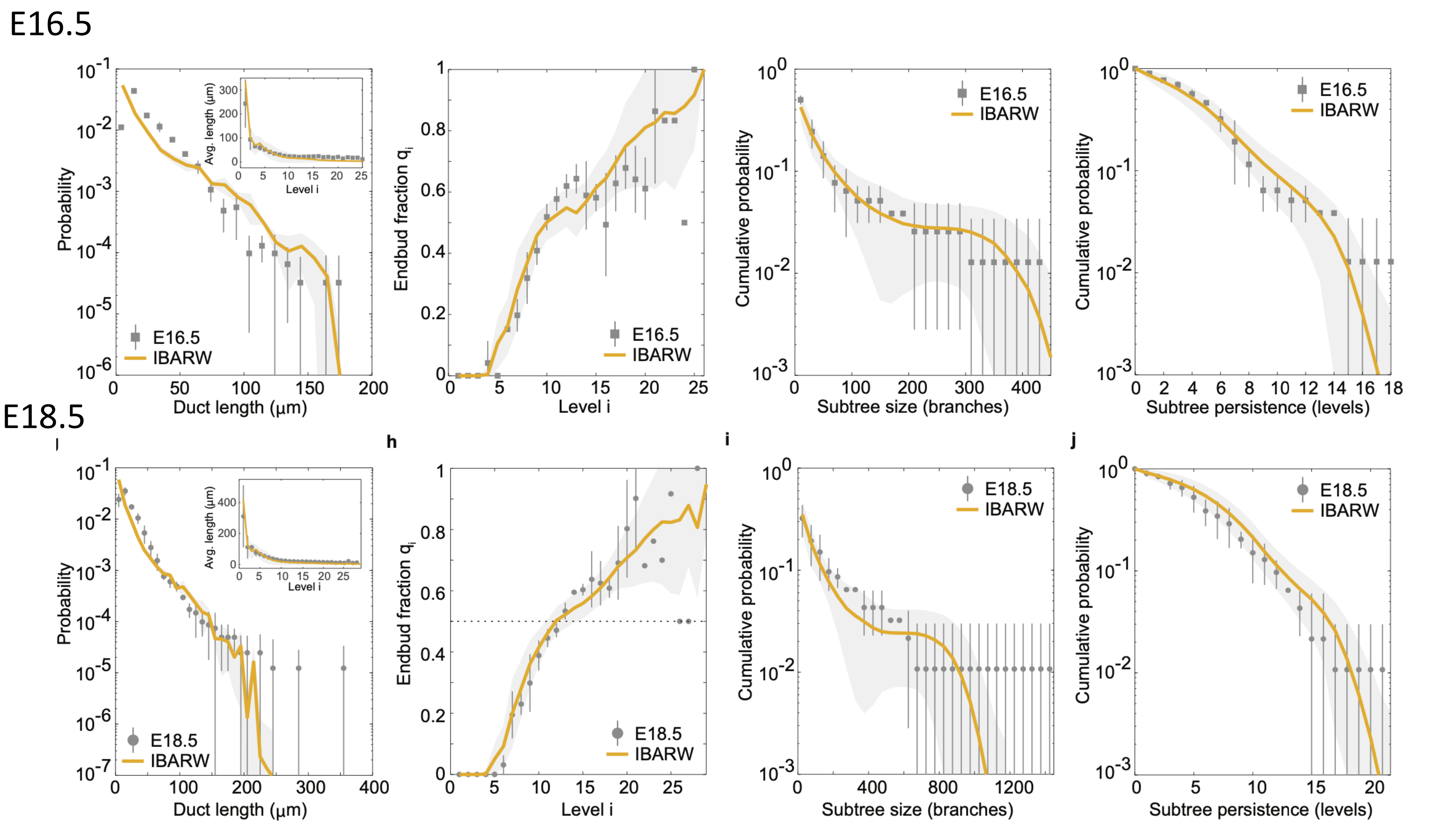






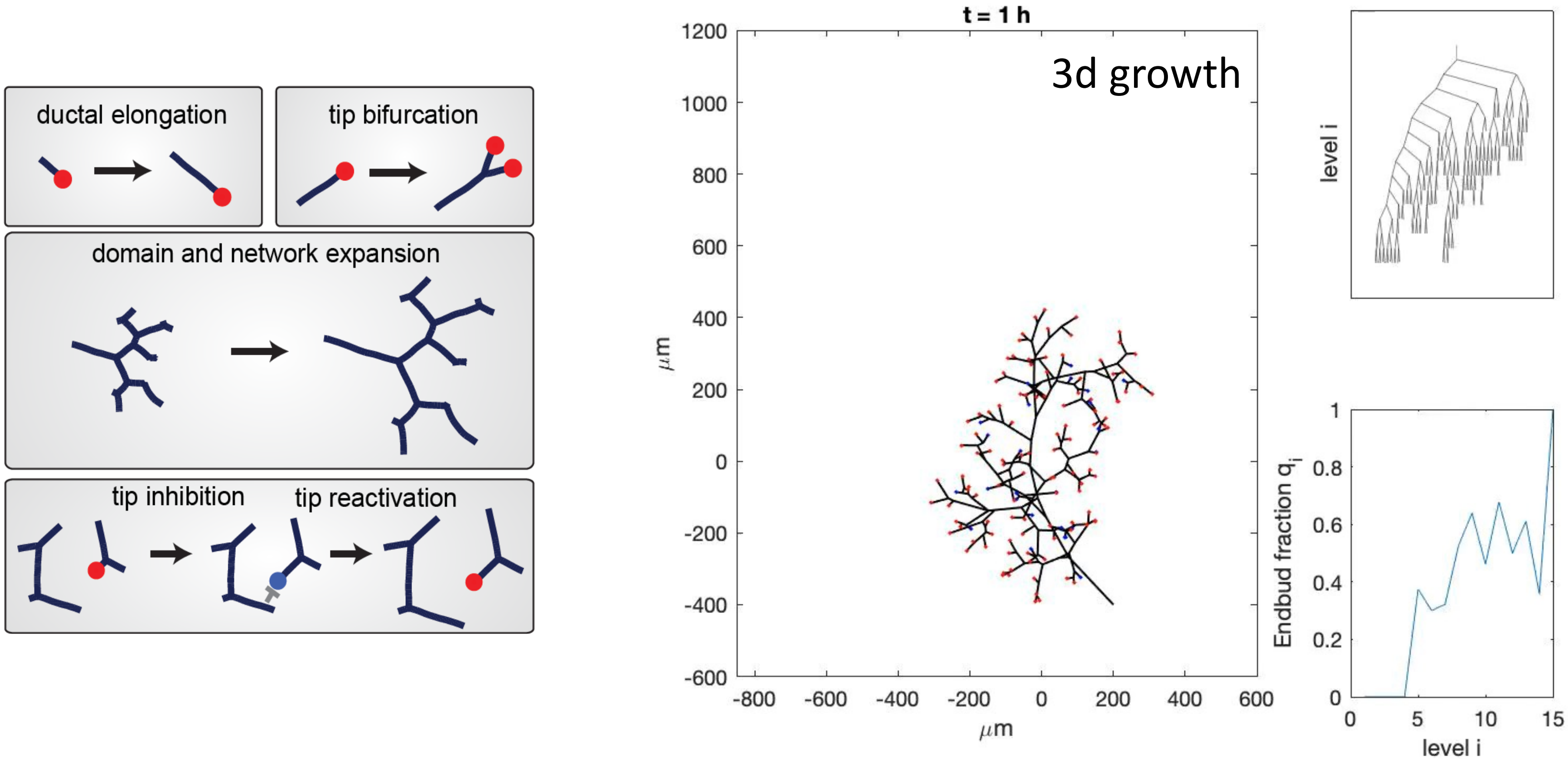
Parameter	Empirical/Fit	Value for simulations of E16.5/E18.5
R_{branch} (r_{branch})	Empirical	0.05 h^{-1} (0.45)
R_{exp} (r_{exp})	Best fit	0.006 h^{-1} (0.054)
R_{a}	Best fit	45 μm
Initial condition	Empirical	Rudimentary tree at E14.5 (see Fig. S3a-S3c)
Simulation time	Empirical	48/84 h
Duct tortuosity (Δ)	Empirical	0.11
Branch angle α (Fig. S6a-S6d)	Empirical	(Normal Dist.) Mean: $90°$ SD: $20°$
Branch angle φ (Fig. S6a-S6e)	Empirical	(Laplace Dist.) Mean: $90°$ b: $21°$

The model recapitulates spatial and topological features of the tissue



Consistency!

Branching morphogenesis is driven by tissue inflation



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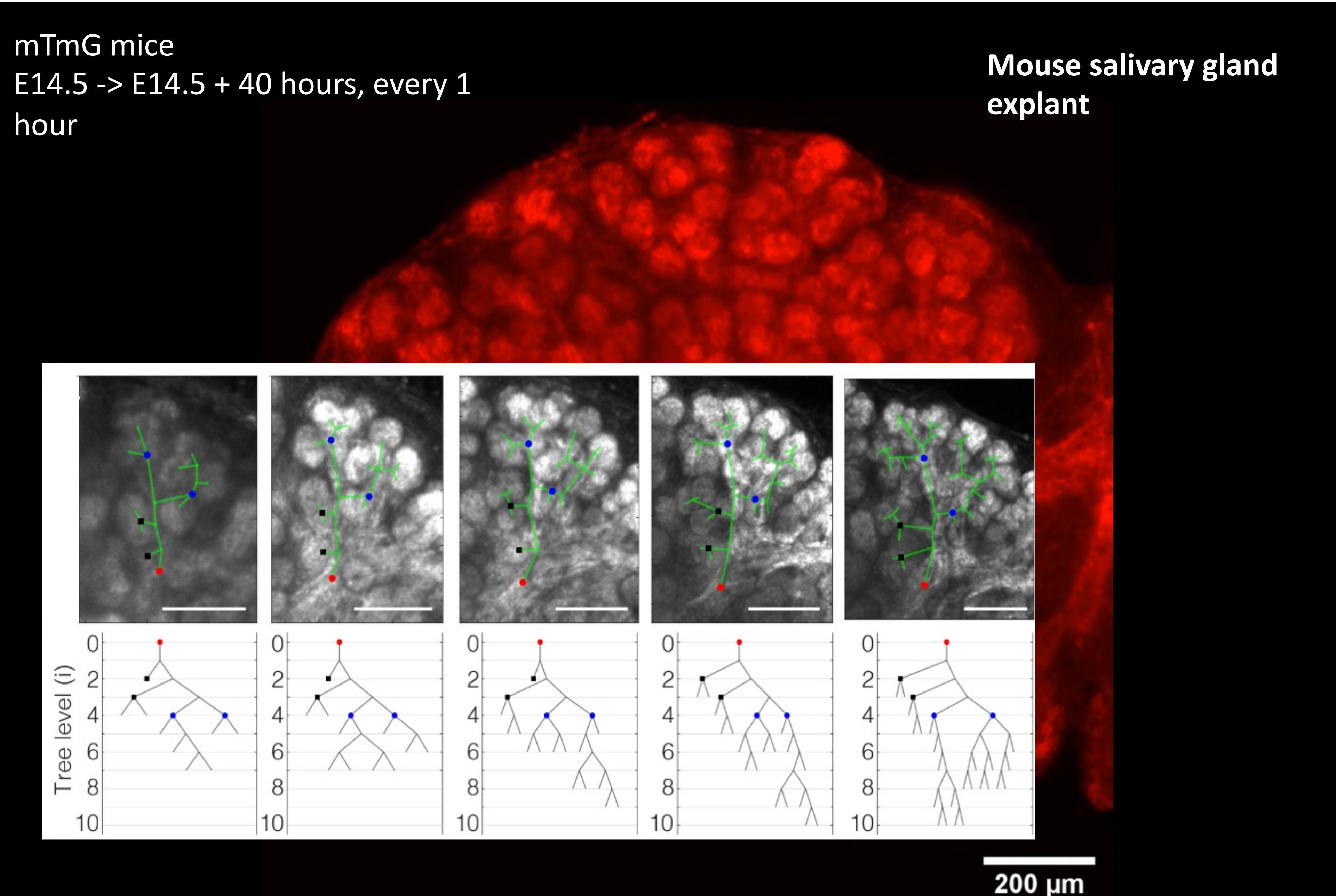
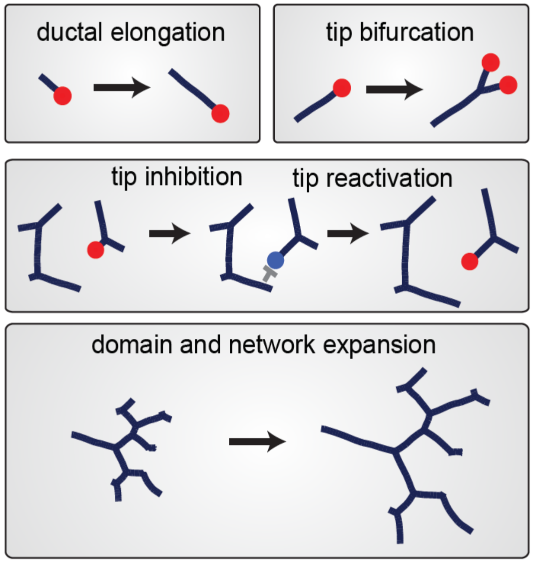
Model prediction: lower but persistent branching process in the bulk

Salivary gland develops on an expanding domain

Submerged tips branch slower than peripheral



Mean-field description of the inflationary branching-delayed random walk



$a \xrightarrow{R_{\text{branch}}} a + a$	branching
$a \xrightarrow{R_{\text{elong}}} a + i$	duct formation
$i \xrightarrow{R_{\text{exp}}} i + i$	duct elongation
$a + i \xrightarrow{R_{\text{inhib}}} s + i$	tip termination
$a + a \xrightarrow{R_{\text{inhib}}} s$	tip termination
$a + s \xrightarrow{R_{\text{inhib}}} s + s$	tip termination
$s \xrightarrow{R_{\text{exp}}} a$	tip reactivation

a: active tips

s: delayed tips

i: inactive ducts

<u>Mean-field level</u>

$$\frac{\partial A}{\partial t} + \nabla \cdot (\mathbf{u}A) = D\nabla^2 A + R_{\text{branch}} A - R_{\text{inhib}} A(A + I + S) + R_{\text{exp}} S$$

$$\frac{\partial S}{\partial t} + \nabla \cdot (\mathbf{u}S) = R_{\text{inhib}} A(A + I + S) - R_{\text{exp}} S$$

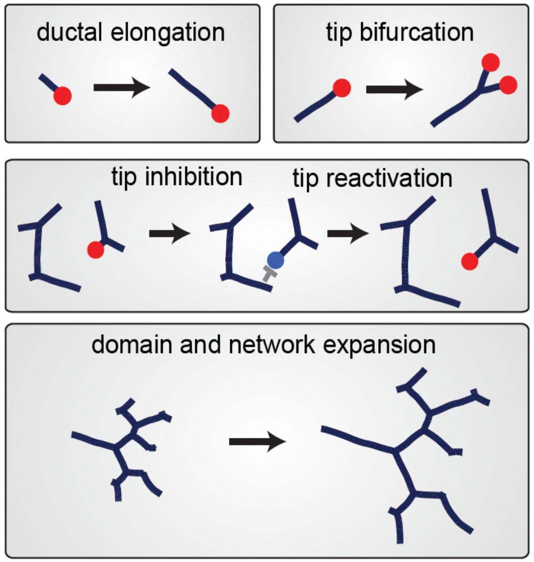
$$\frac{\partial I}{\partial t} + \nabla \cdot (\mathbf{u}I) = R_{\text{exp}} I + R_{\text{elong}} A,$$

Advection + dilution

Duct elongation

Tip reactivation

Mean-field description of the inflationary branching-delayed random walk



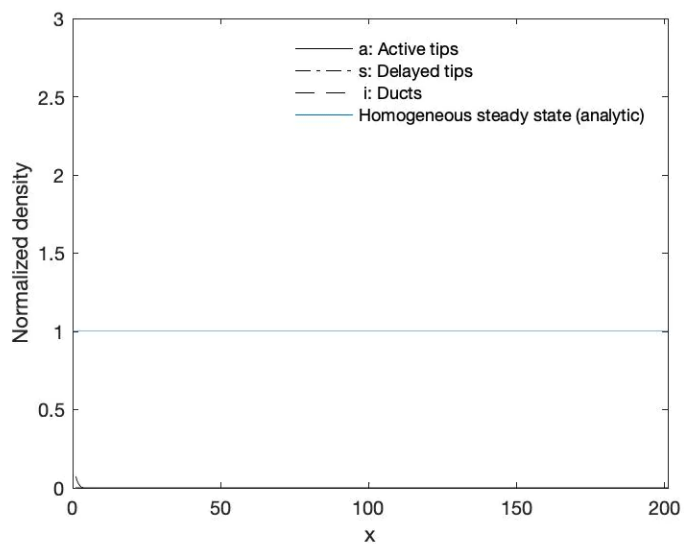
IBARW has an active steady state when $r_{\text{branch}} > dr_{\text{exp}}$

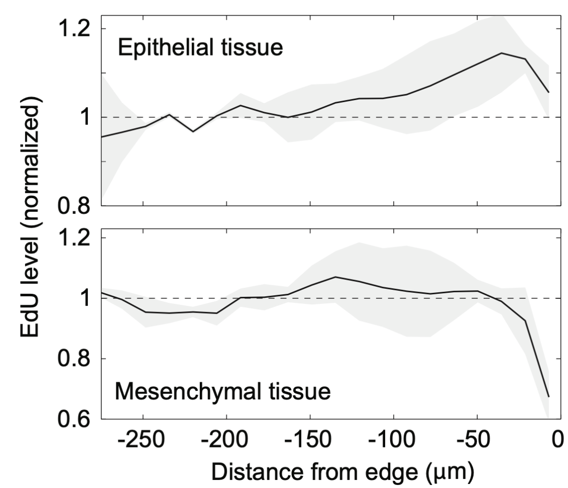
$$A_+ = \frac{r_{\text{exp}}(d^2 - 1)(r_{\text{branch}} - r_{\text{exp}}d)}{r_{\text{branch}}(r_{\text{branch}}d + d - r_{\text{branch}})}$$

$$S_+ = \frac{(r_{\text{branch}} - r_{\text{exp}}d)}{r_{\text{exp}}d}A_+$$

$$I_+ = \frac{1}{r_{\text{exp}}(d-1)}A_+$$

a: active tips
s: delayed tips
i: inactive ducts





Model prediction: Uniform proliferative activity in bulk, increased at the periphery

Defining branching morphogenesis from the cellular to the large scale

How do endbud progenitors regulate the large-scale organization of the tissue?

How do endbud progenitors acquire a specific fate?

Can the large-scale organization emerge from a set of simple rules?

- Tips are locally regulated: branching events are stochastic and uncorrelated.
- Tissue inflation drives the growth process by allowing submerged tips to continue branching.
- Branching can compensate for the tissue “dilution” due to inflation, allowing for a non-trivial stable stationary steady state.

Chatzeli L*, Bordeu I* *et al., Dev. Cell*. 2023

Bordeu I*, Chatzeli *et al., Nat. Commun* in press

Defining branching morphogenesis from the cellular to the large scale

How do endbud progenitors regulate the large-scale organization of the tissue?

Can the large-scale organization emerge from a set of simple rules?

How do endbud progenitors acquire a specific fate?

(some) Open questions

- How do tips retain their self-renewing potential through serial rounds of branching?
- How are "delay" and permanent arrest regulated.
- Which are the drivers of tissue inflation?
- What does the postnatal dynamic look like?

Chatzeli L*, Bordeu I* *et al., Dev. Cell*. 2023

Bordeu I*, Chatzeli *et al., Nat. Commun* in press

Modelling self-organisation in Developmental Biology

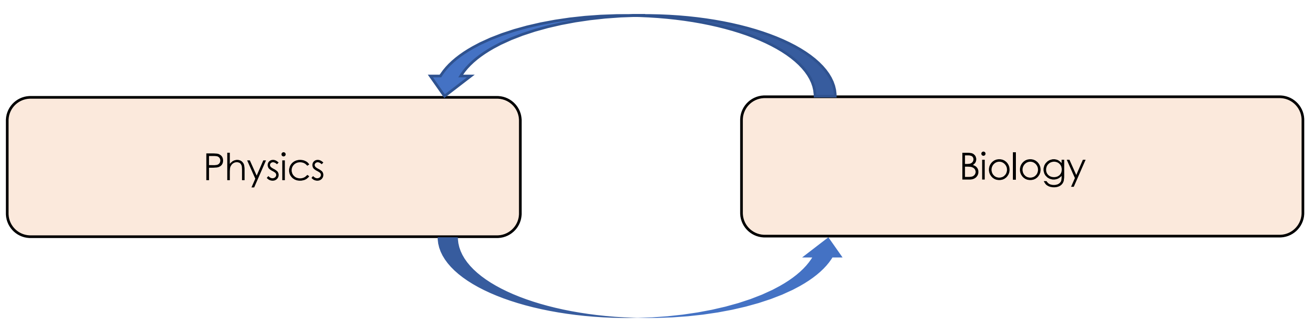
Take home message:

1.**Mathematical and physical models can help simplify biological systems**, allowing scientists to gain insights into their behavior and underlying principles.

2. **Models can be used to make predictions** about biological systems, which can then be tested experimentally.

3. **Models can help interpret experimental data** by providing a framework for understanding how different variables interact within a system.

Physics inspired by biology



Biology inspired by physics