

From large image datasets to scientific insights in developmental biology

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CENTURI – LIS (QARMA)
GDR ADN annual meeting
March 28, 2019

Developmental biology

From a single fertilized cell to a complex organism



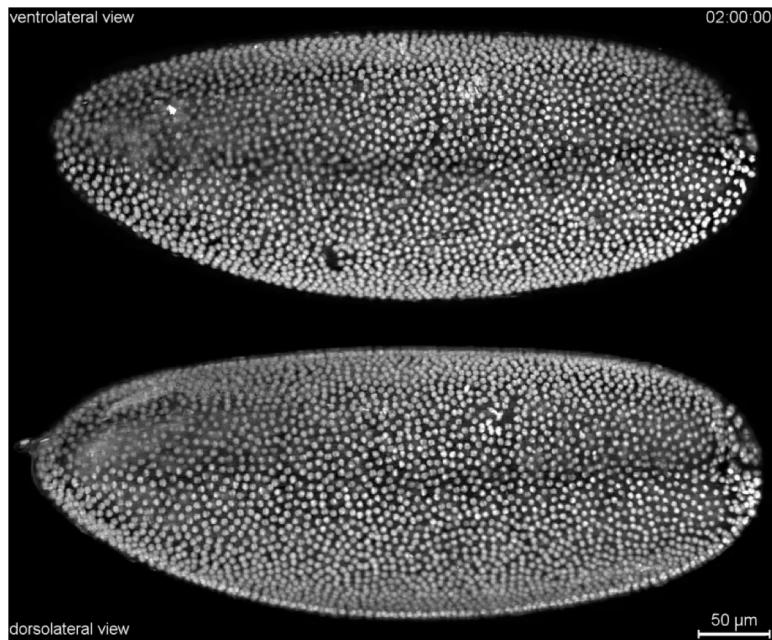
Zebra Fish – *Danio rerio*



Swinburne et al., PLoS One, 2015

A multiscale process

Microscopy reveals cell behaviors ..

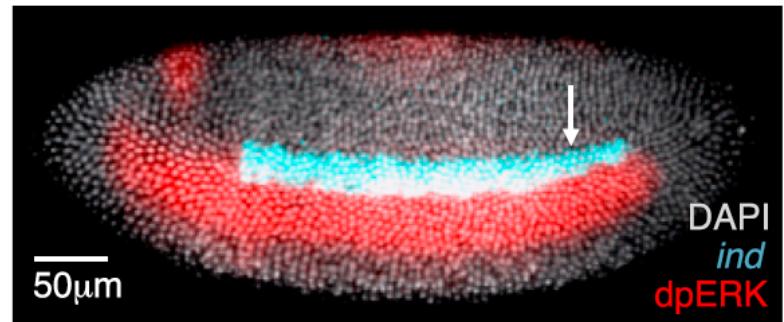


Tomer et al., *Nature Methods*, 2012



Fruit Fly – *Drosophila melanogaster*

.. and changes in patterns of gene expression



Lim et al., *Current Biology*, 2015

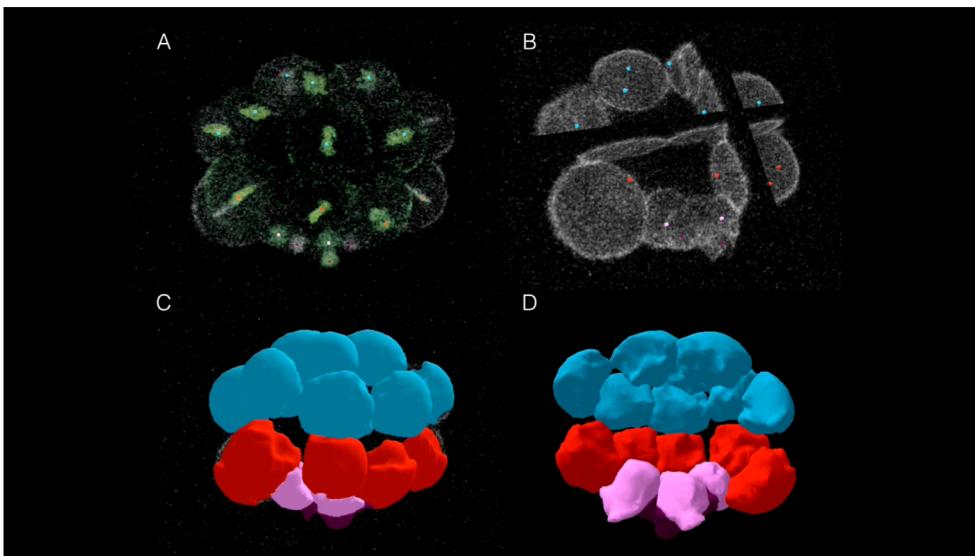
Many heterogenous components in interaction
Coupled levels of organization
Path-dependency

Requires multidisciplinary efforts

An integrative approach

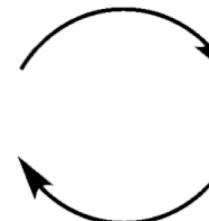


From Data ...

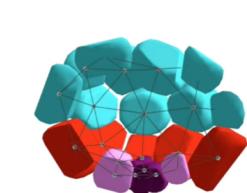
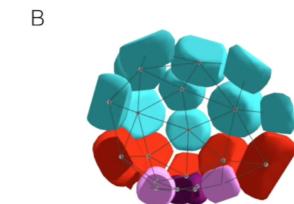
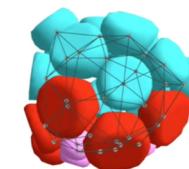
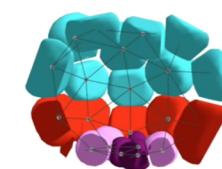


... To Biomechanical Modeling

Statistical Modeling

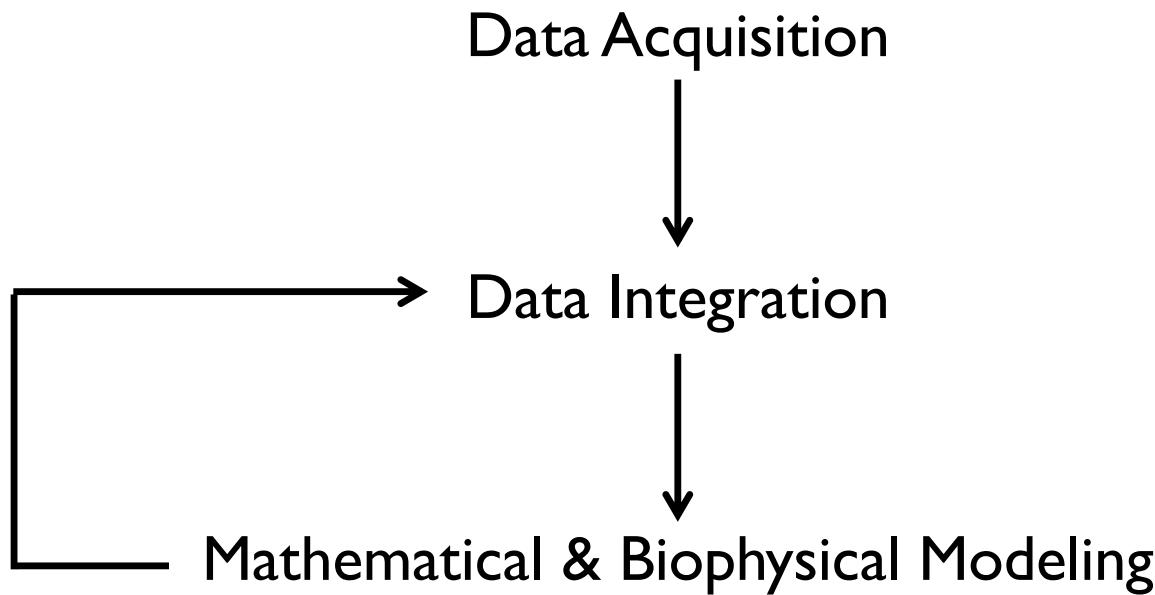


Quantitative
Comparison



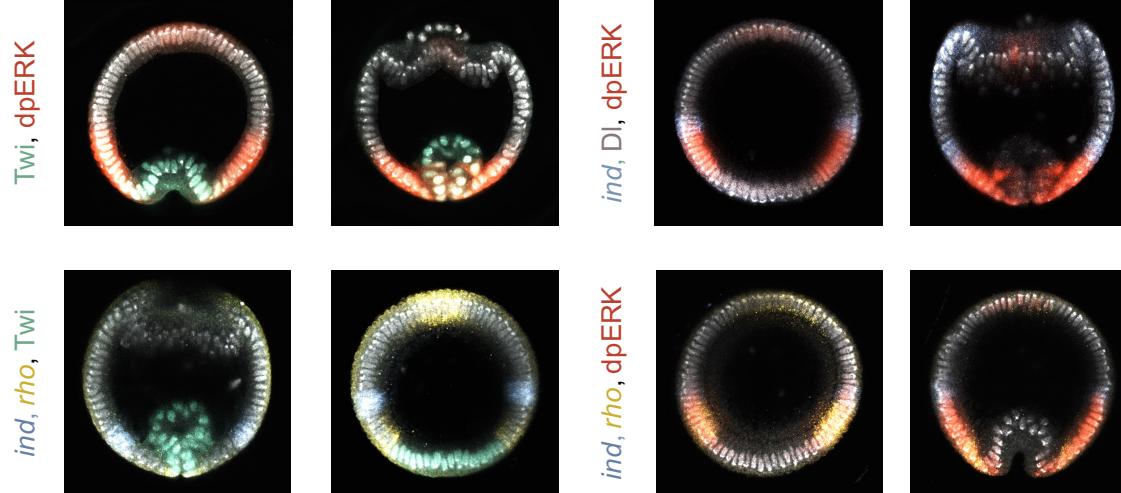
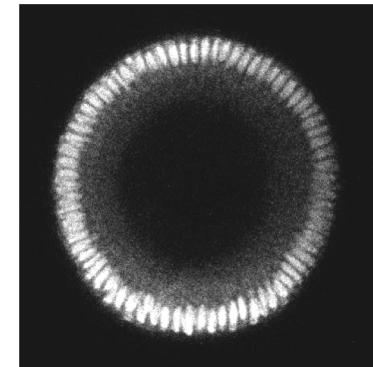
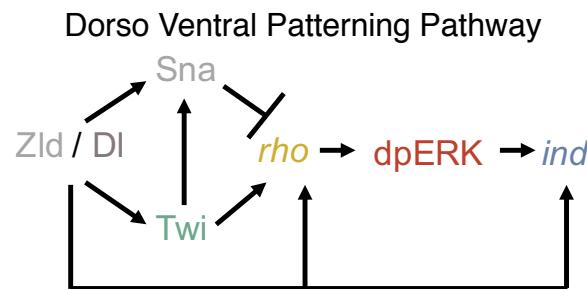
Villoutreix et al., Sci. Rep., 2016

A generic methodological framework

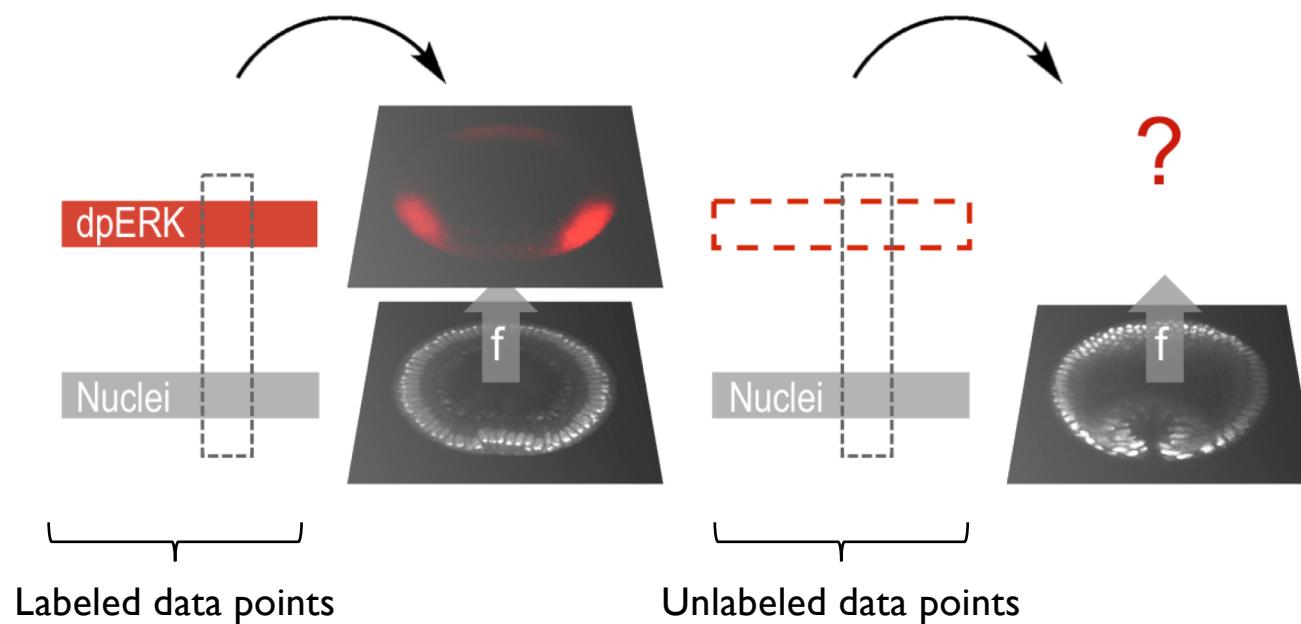


Can we use the same framework for studies of signaling dynamics?

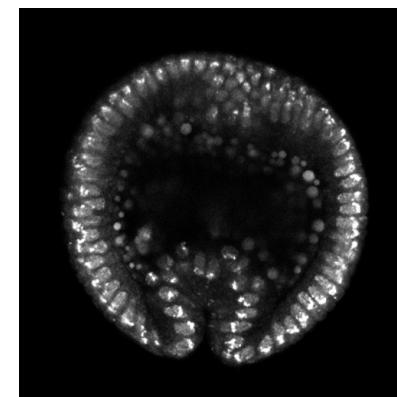
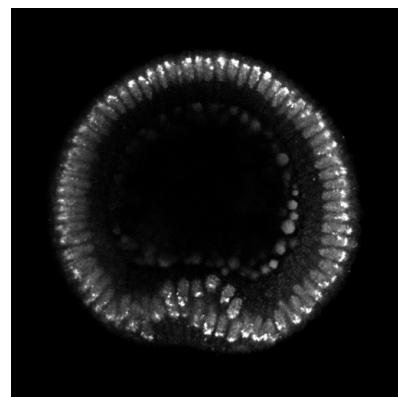
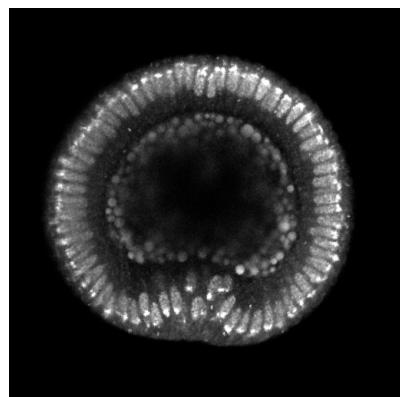
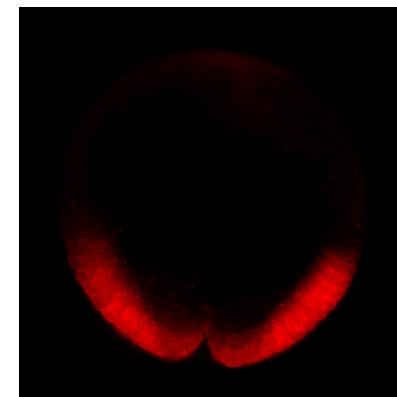
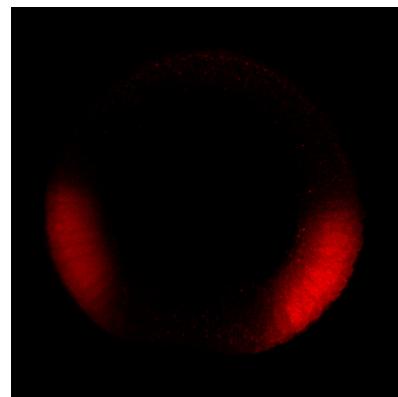
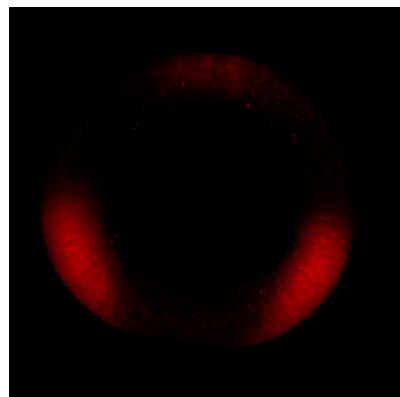
How to study pattern formation with many variables



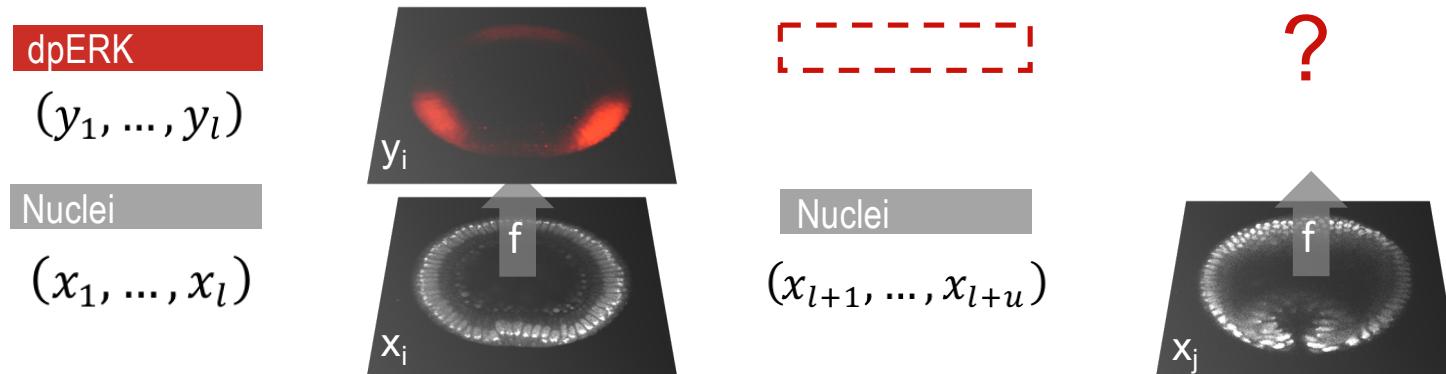
Learning a mapping between morphology and patterns of gene expression



Similar morphologies lead to similar patterns of gene expression



Transductive learning as a global optimization problem

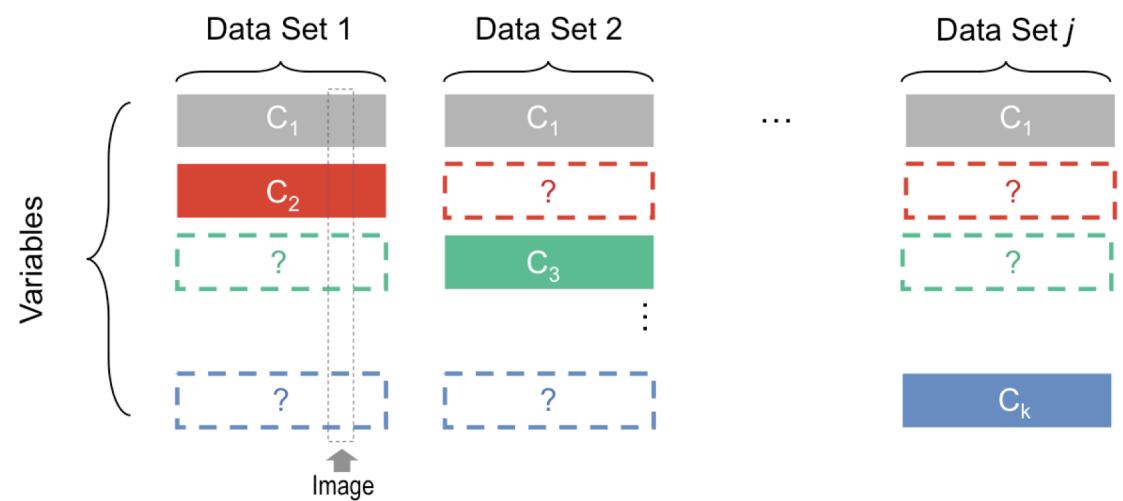
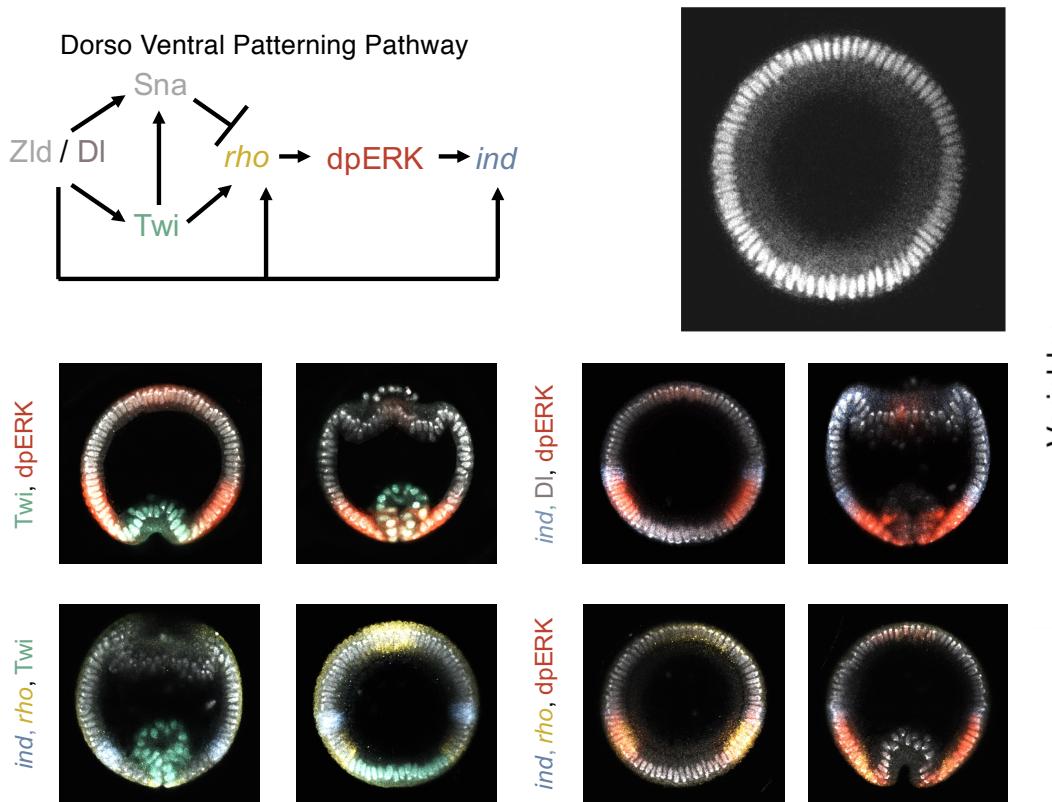


Find f such that $y = f(x)$ and

$$\arg \min_{\substack{f \in \mathcal{Y}^{l+u} \\ \forall i \leq l \quad f(x_i) = y_i}} \sum_{i,j=1}^{l+u} w_{i,j} \left(f(x_i) - f(x_j) \right)^2$$

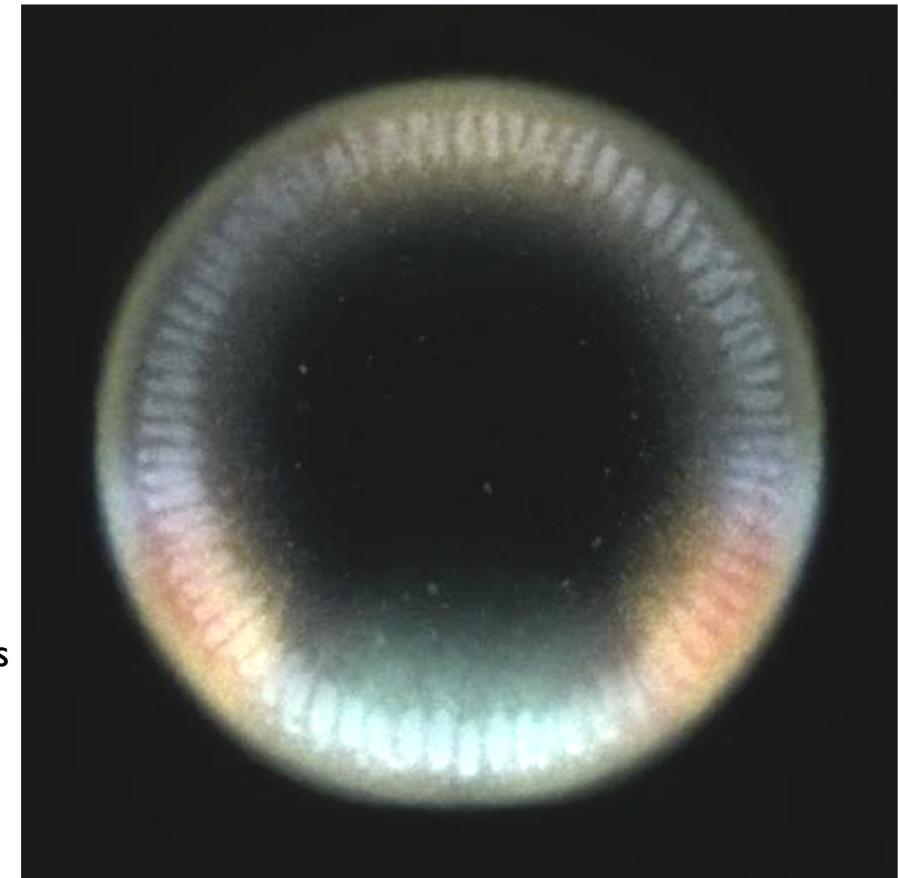
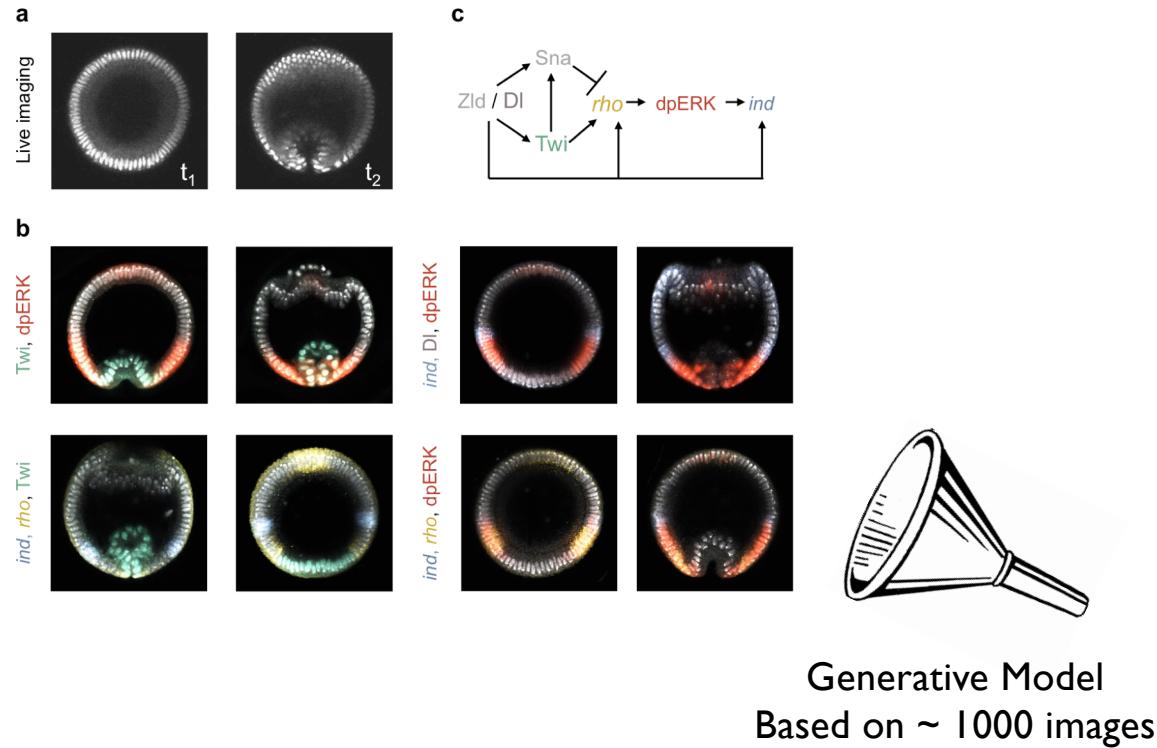
where $w_{i,j} = \exp \left(-\frac{\|x_i - x_j\|^2}{2\sigma^2} \right)$

Integrating all the variables

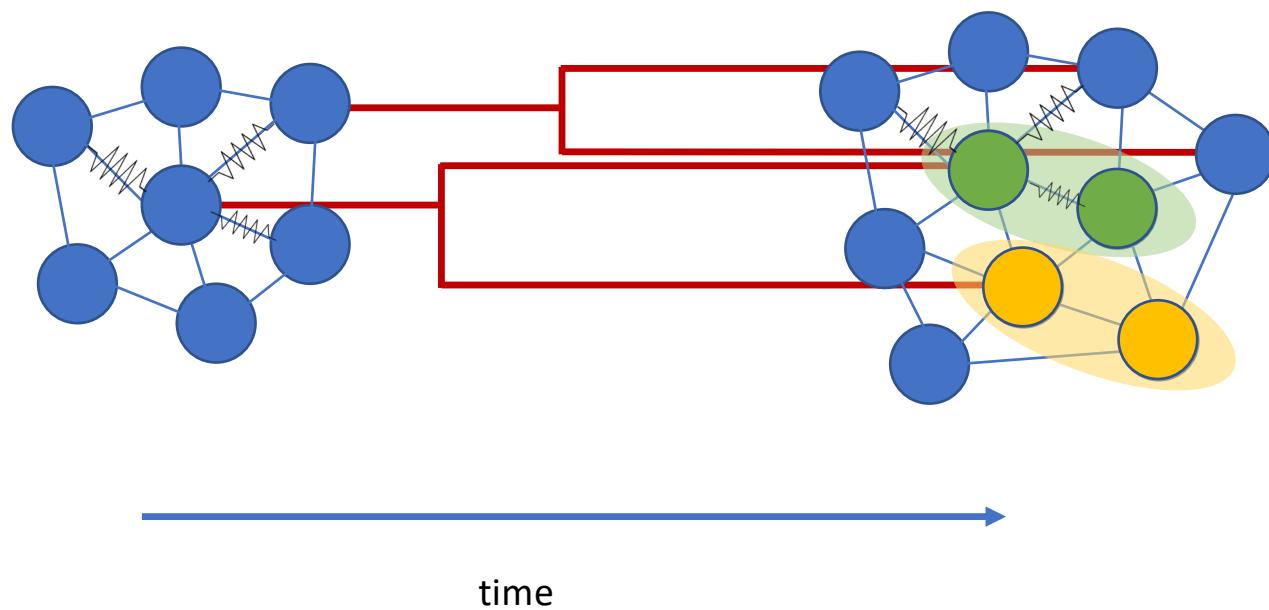


Data fusion amounts to complete the matrix

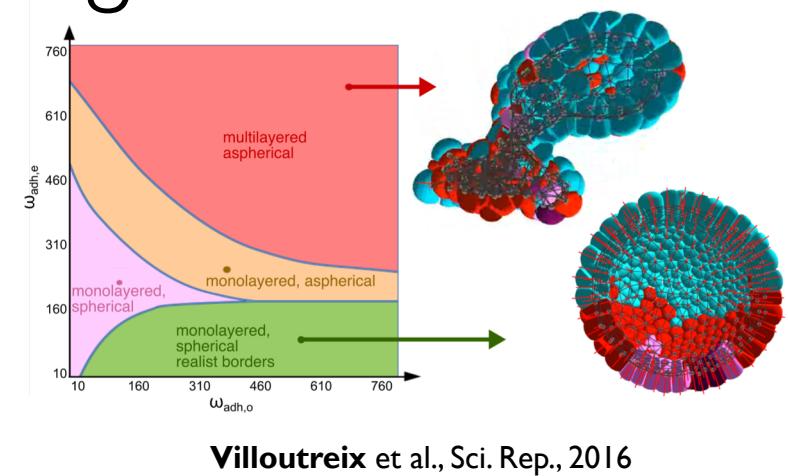
An accurate movie is obtained by data fusion



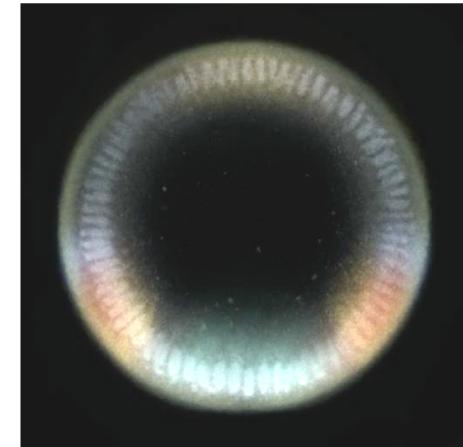
Correlating patterns formation with biomechanical modeling from data



What are the morphogenetic constraints induced by the cell lineage?

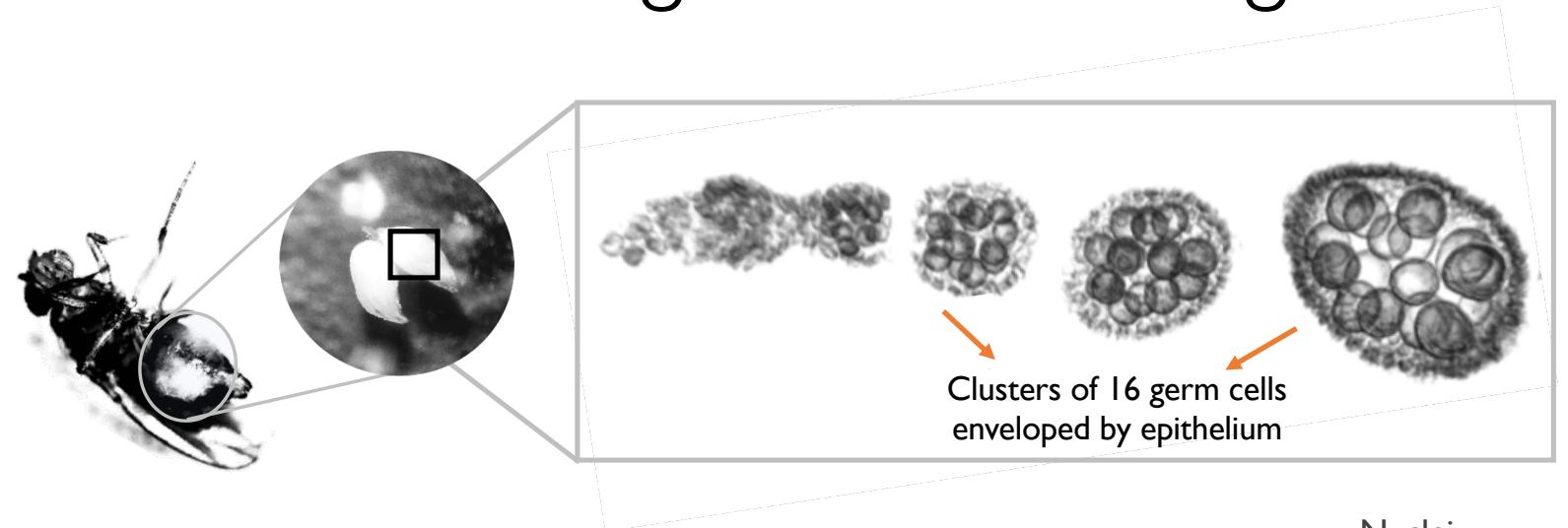


Villoutreix et al., Sci. Rep., 2016

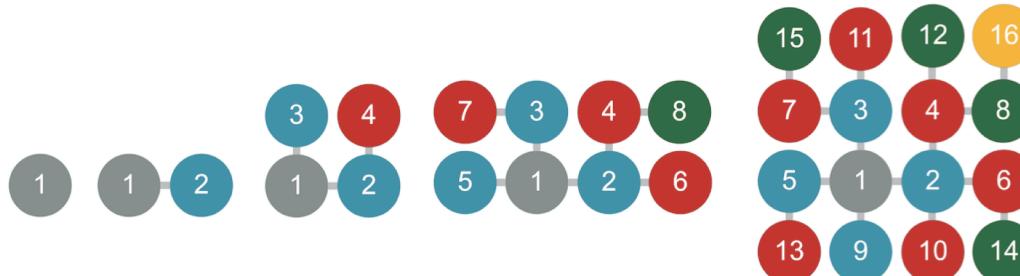


Villoutreix et al., PLoS Comp. Biol., 2017

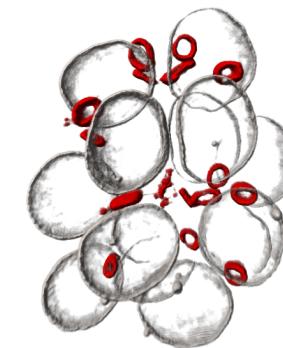
Cell Lineage Tree Packing



16-cell cyst arises from 4 stereotypic (incomplete) divisions



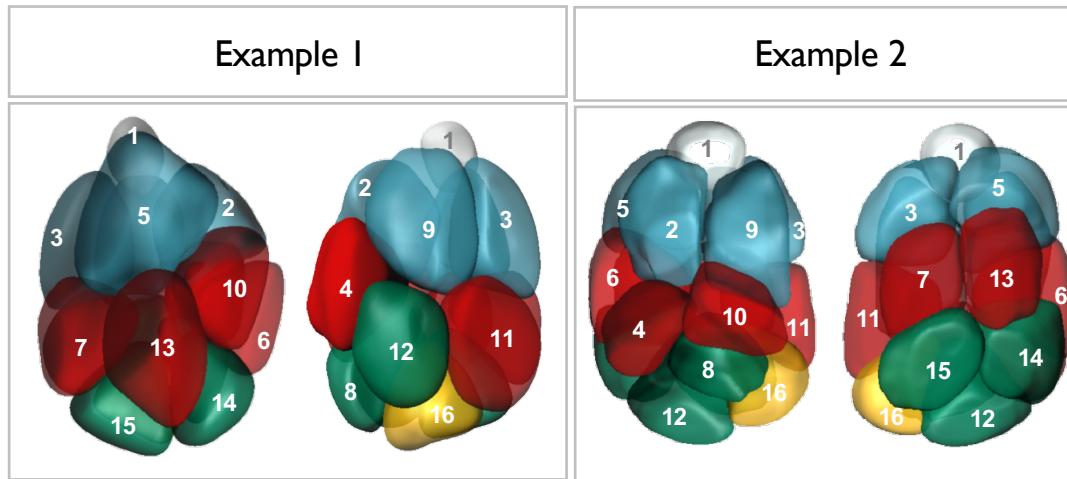
Nuclei
Cytoplasmic bridges



Can we characterize the various packing arrangements of the 16 cells?

Imran Alsous*, Villoutreix*, Stoop* et al., Nature Physics, 2018

Visualizing Packing: Imaging & Reconstructions



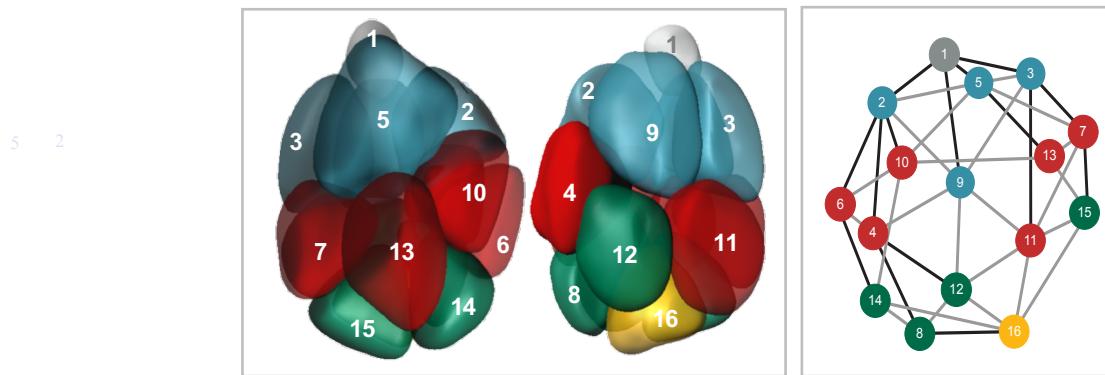
Unambiguous identification & annotation of each cell across cysts

Cell connected directly through ring canals and contact through membrane contacts

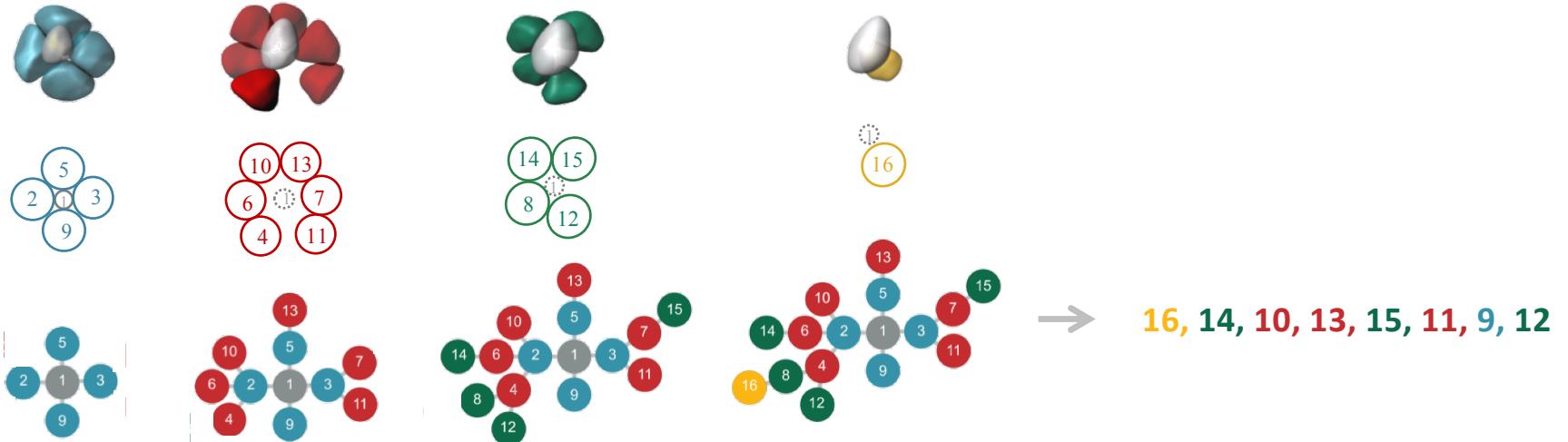
No central cell: all contact outer epithelium

Note cells' layered organization and variation in the intra-layer organization

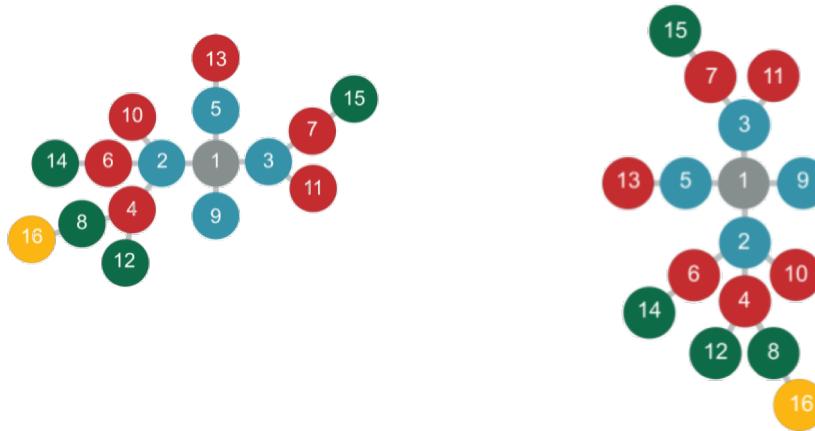
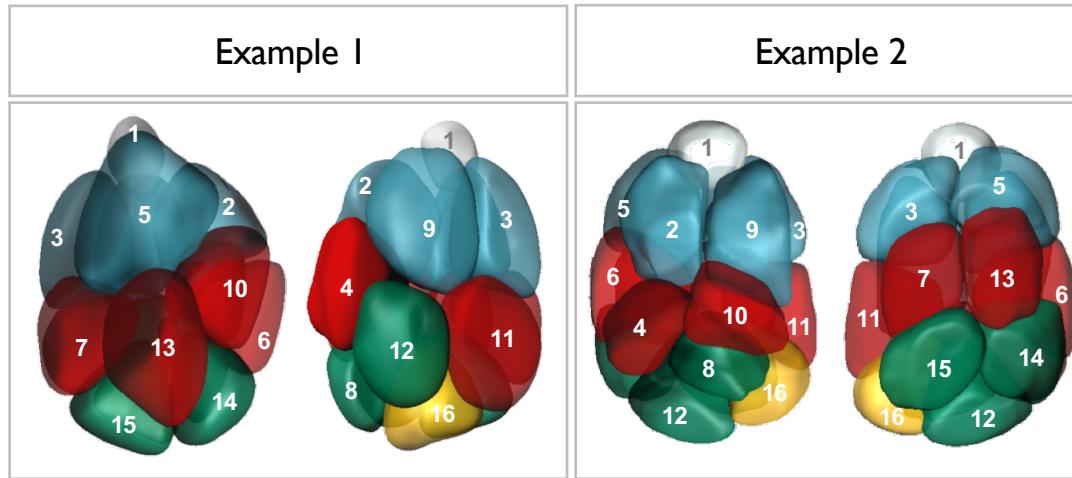
3D Organization to 1D Descriptor



Decoding organization by characterizing how the cell lineage tree is embedded in the plane



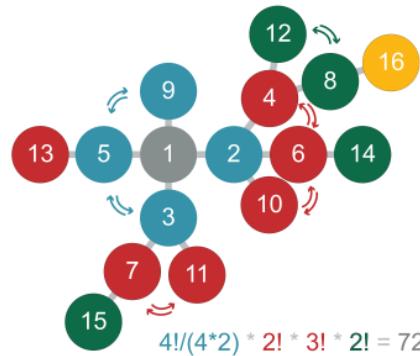
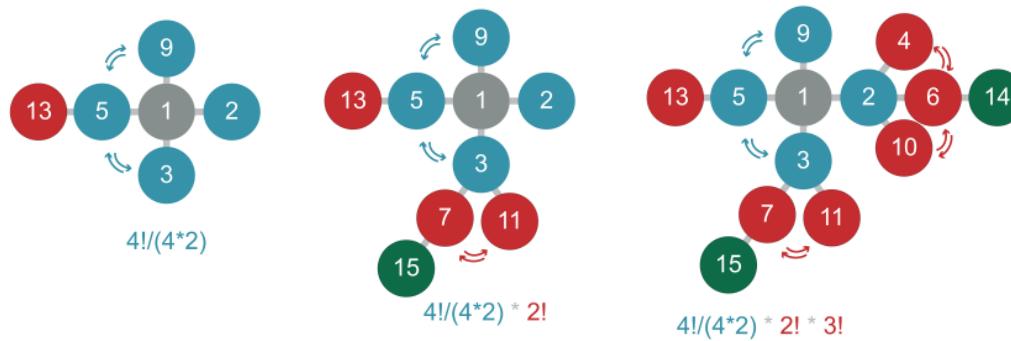
Comparing configurations



16, 14, 10, 13, 15, 11, 9, 12

16, 12, 14, 13, 15, 11, 9, 10

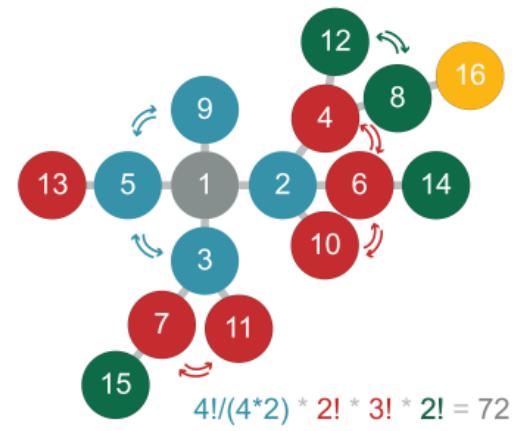
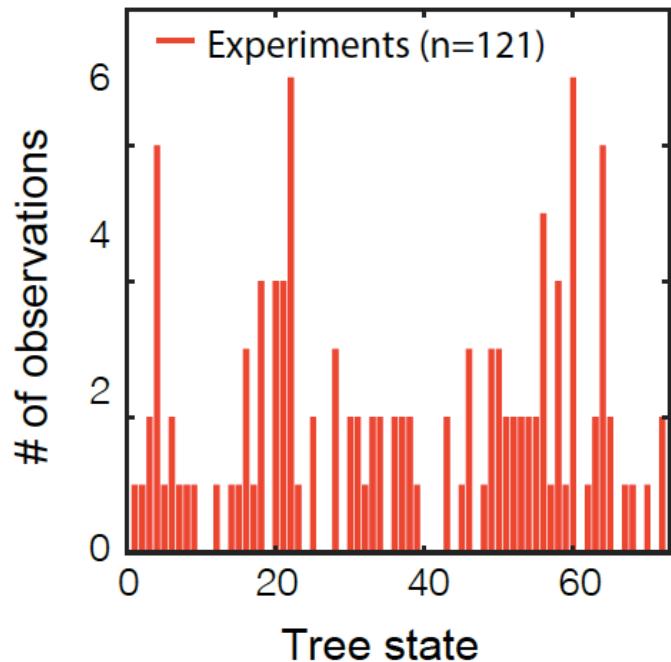
72 configurations



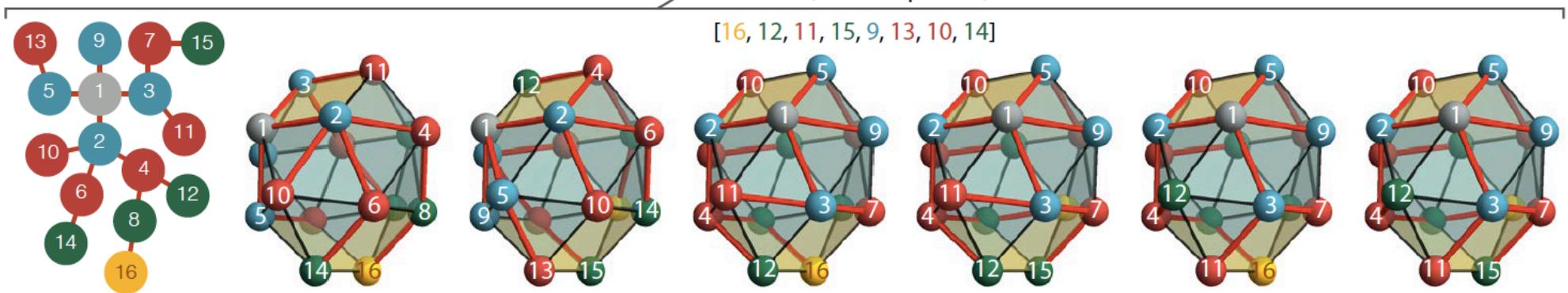
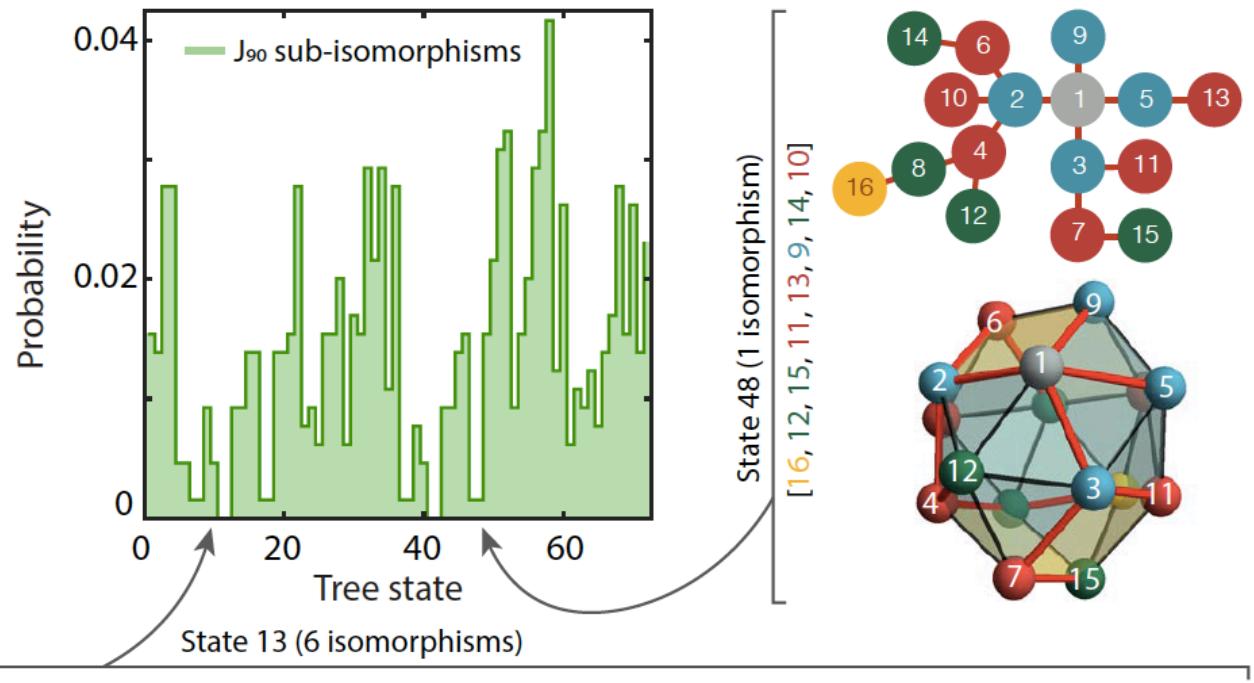
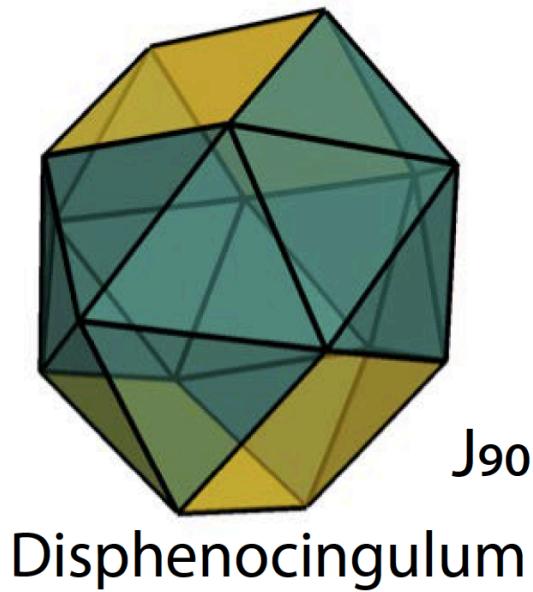
Accounting for mirror &
rotational symmetries ...

72

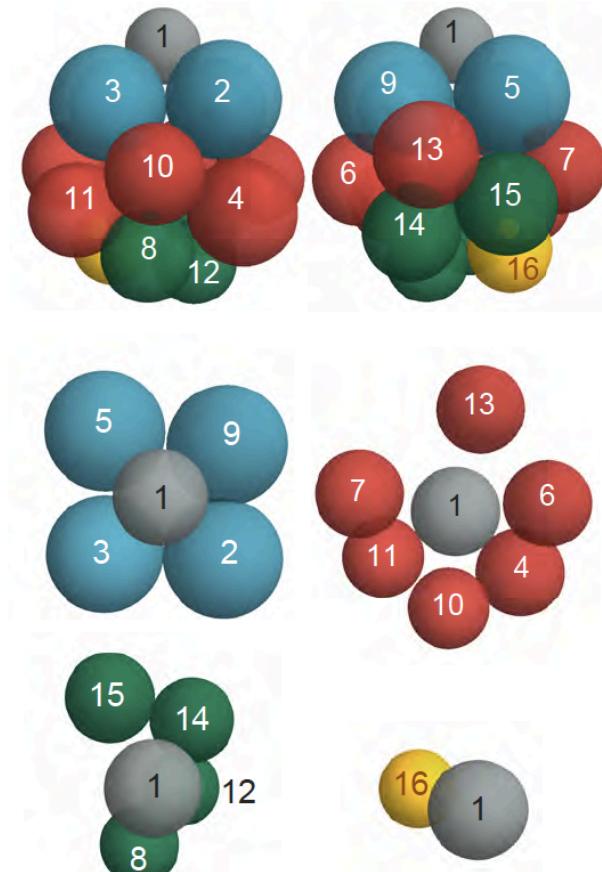
Bias observed experimentally



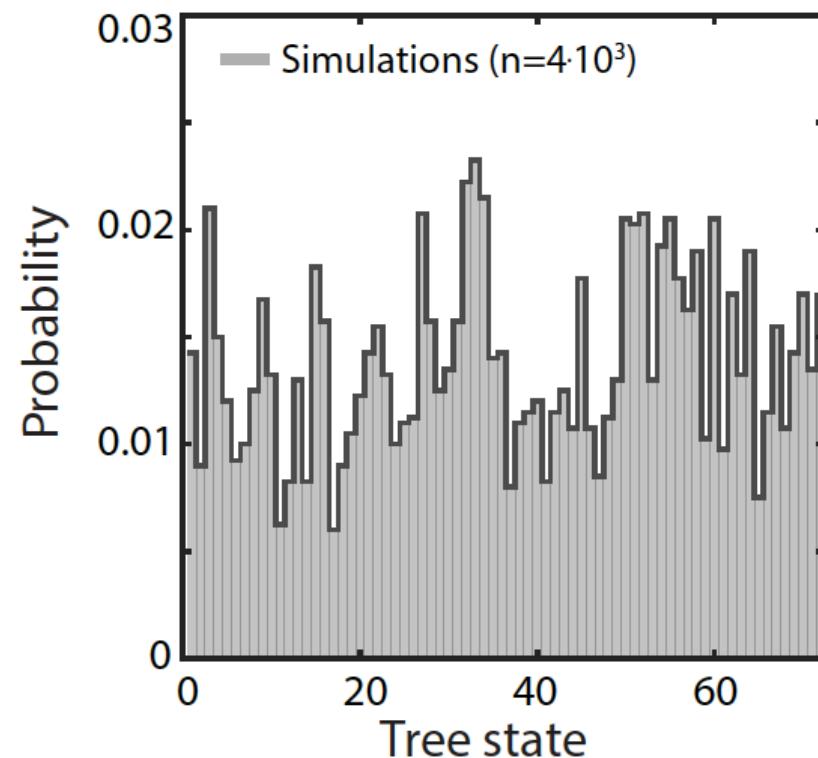
Breaking symmetry



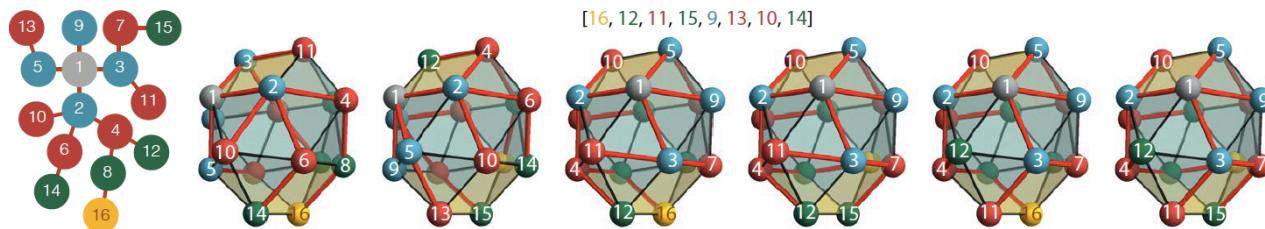
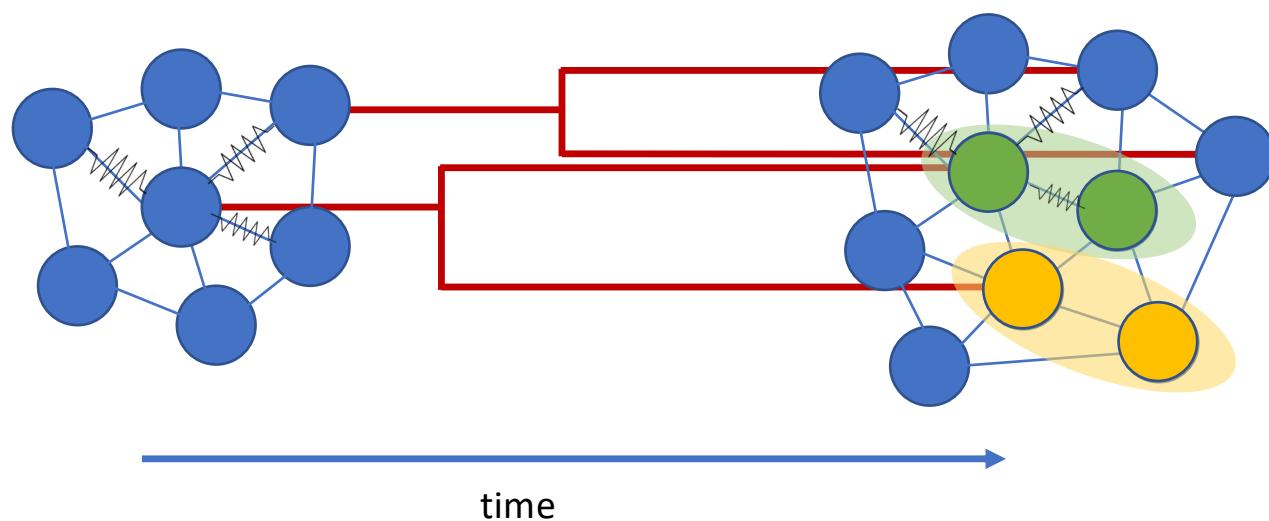
Energy-based models confirm non-uniform cell lineage tree distributions



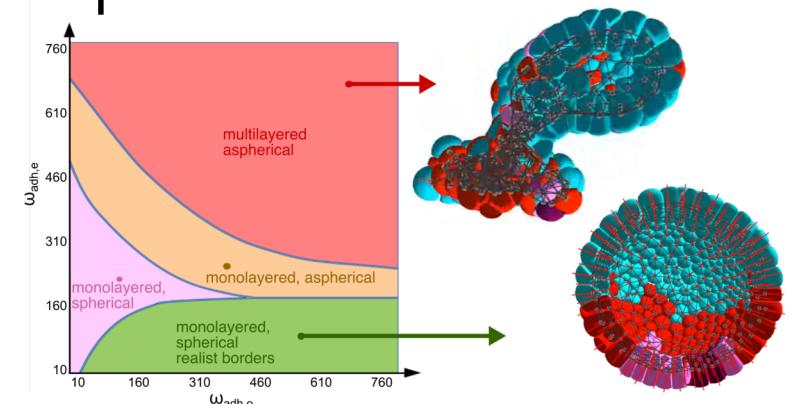
[16, 12, 14, 9, 13, 15, 11, 10]



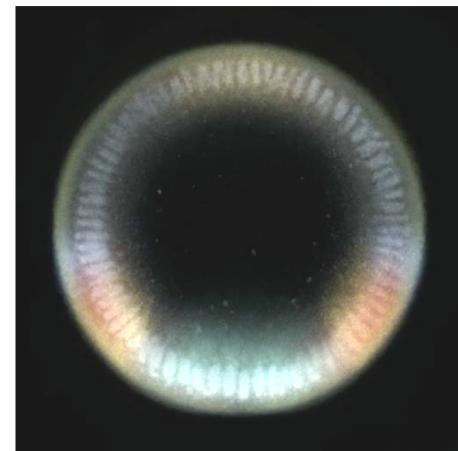
Interplay of biomechanical constraints, signaling dynamics and cell proliferation



Imran Alsous*, Villoutreix*, Stoop* et al., Nature Physics, 2018

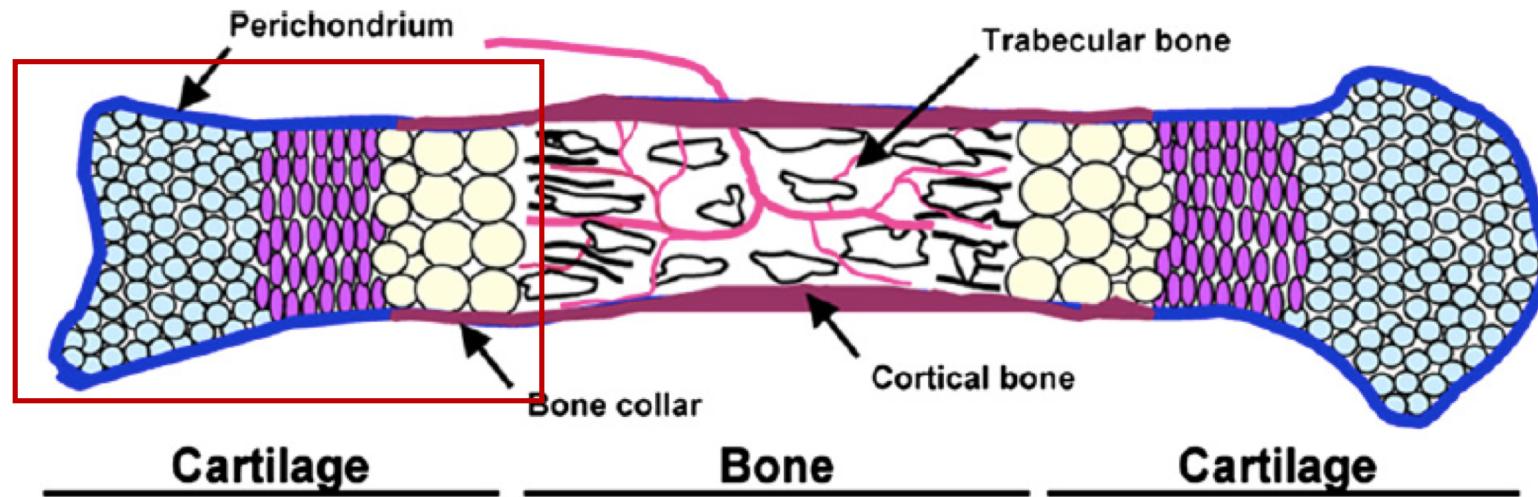


Villoutreix et al., Sci. Rep., 2016

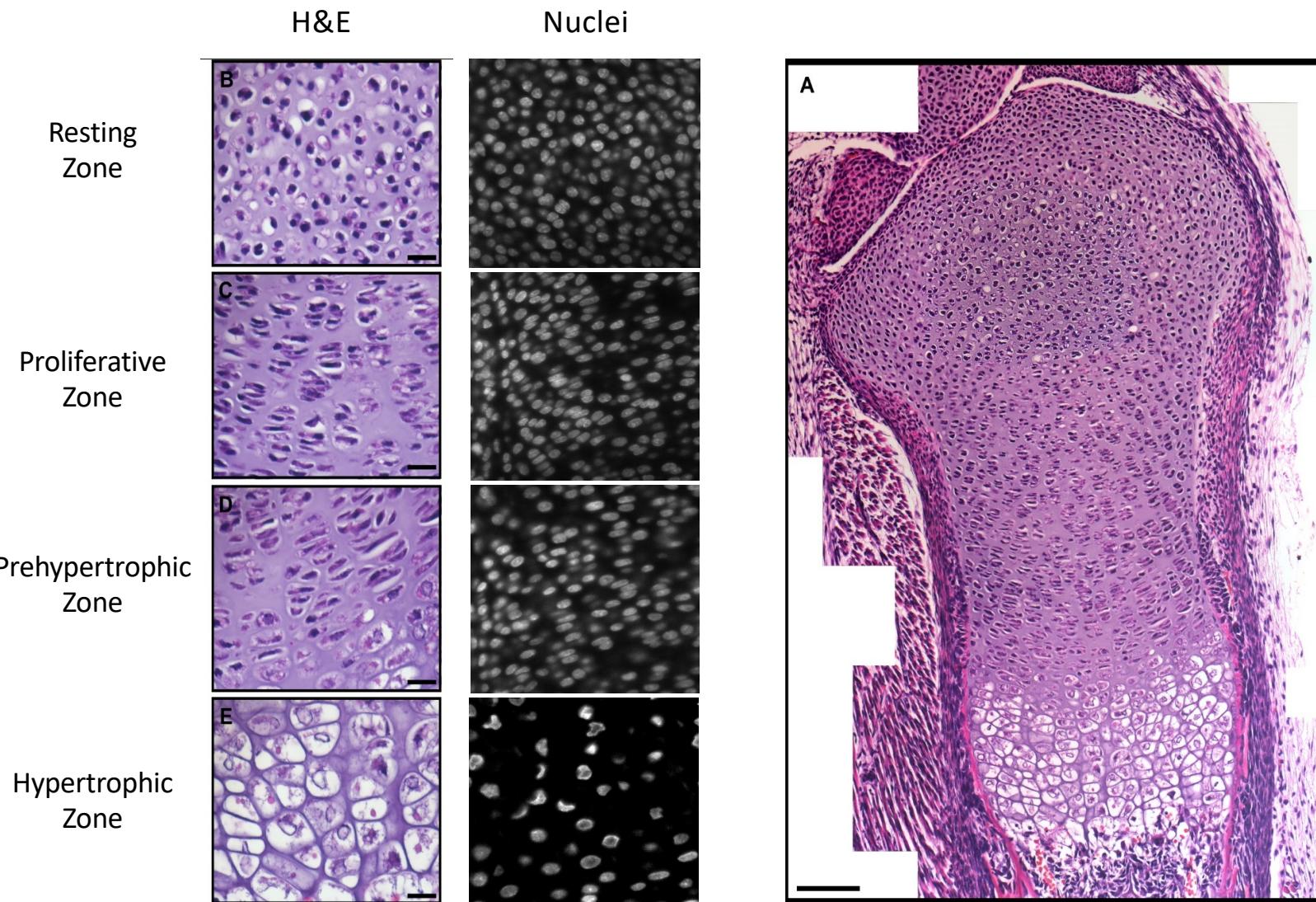


Villoutreix et al., PLoS Comp. Biol., 2017

A more complex tissue: bone morphogenesis

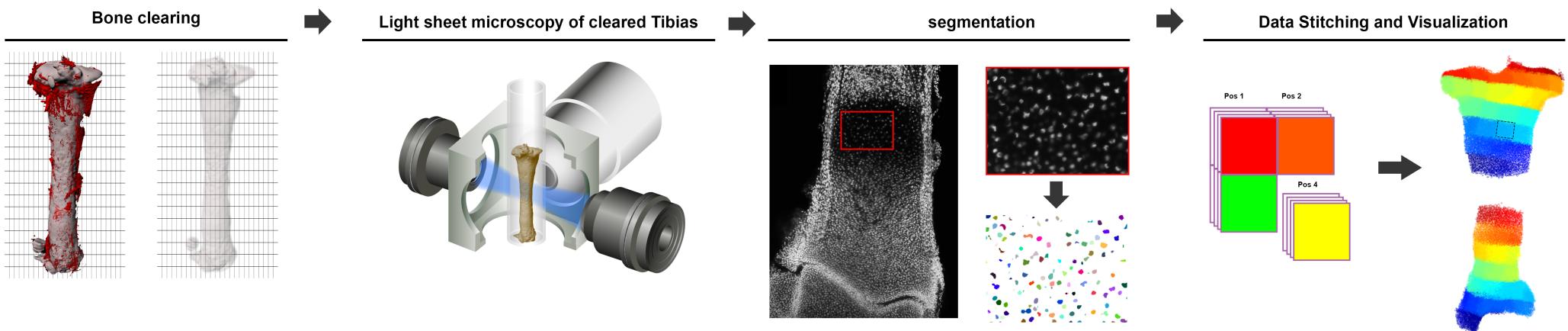


Growth Plate

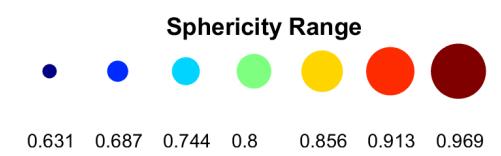
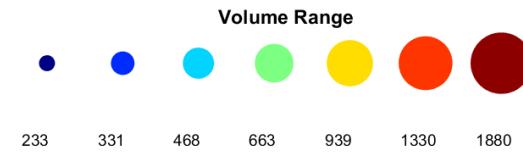
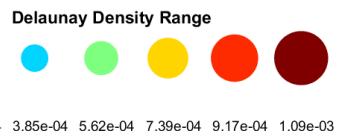
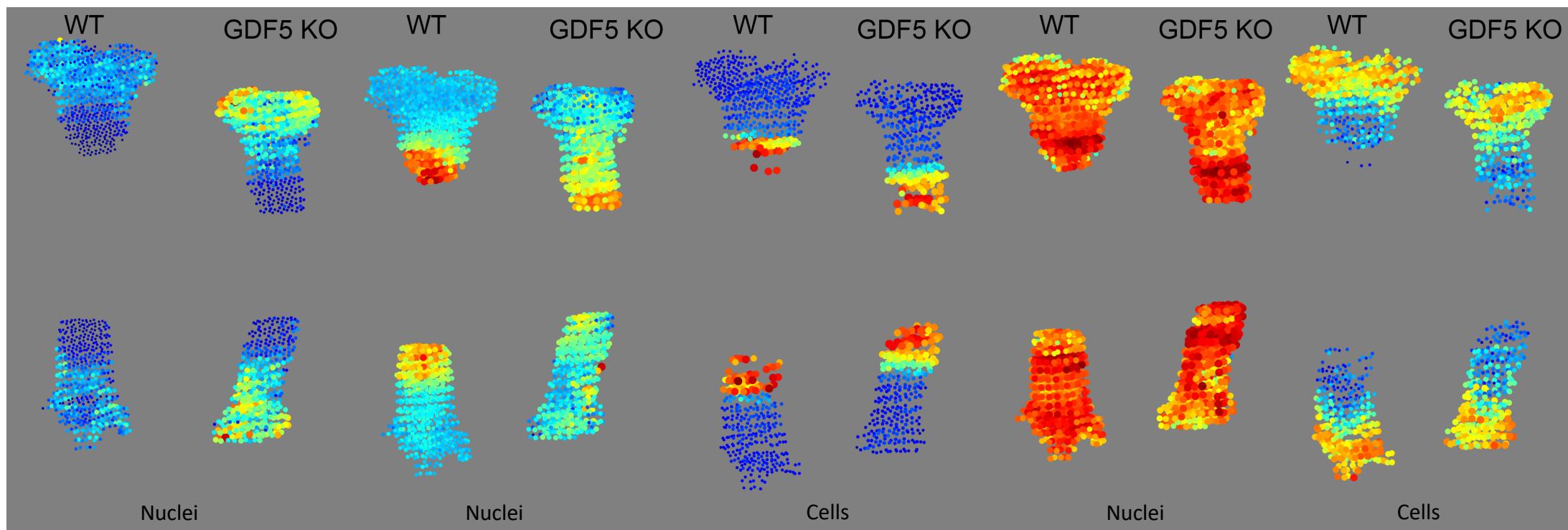


Sarah Rubin

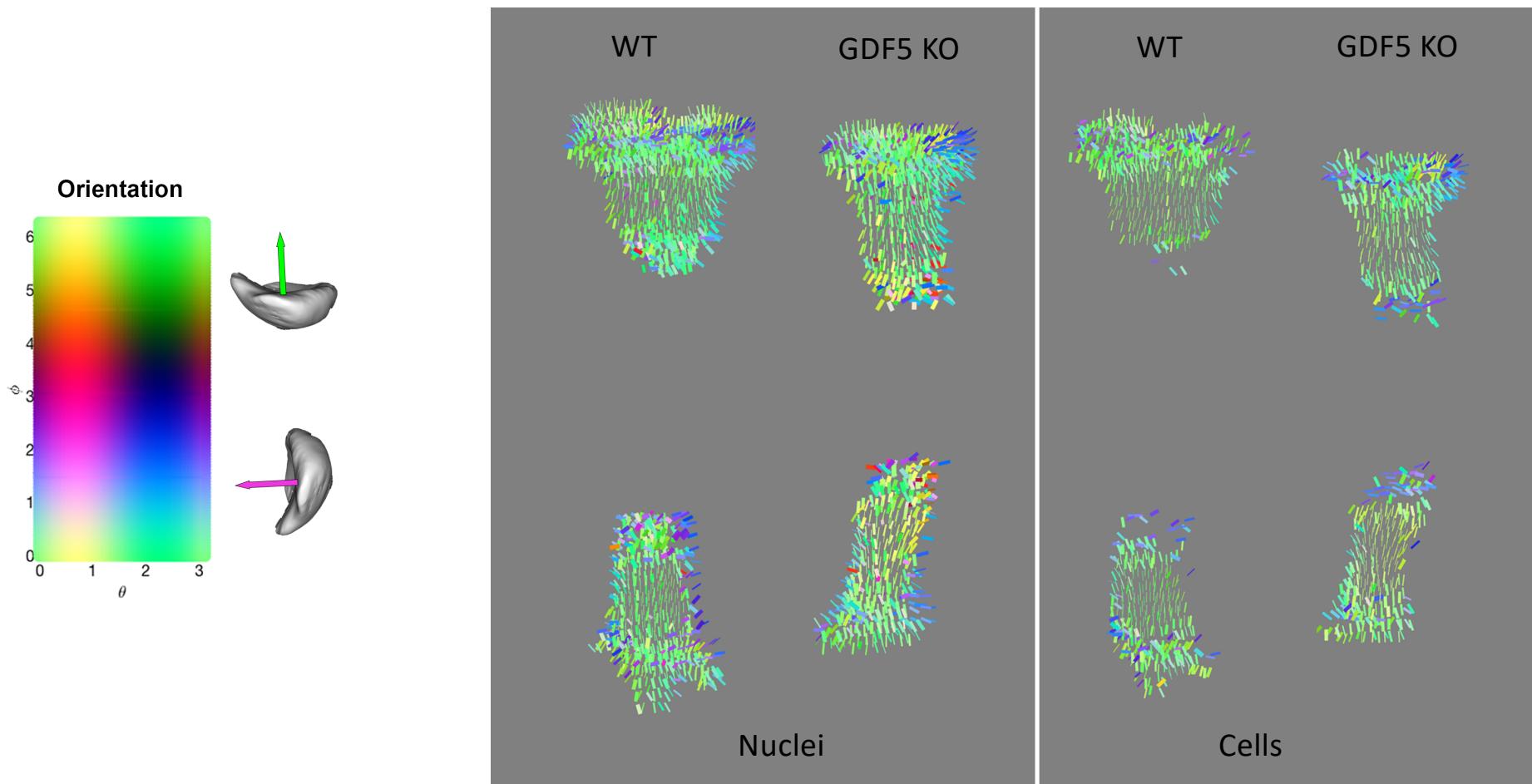
Pipeline for data extraction



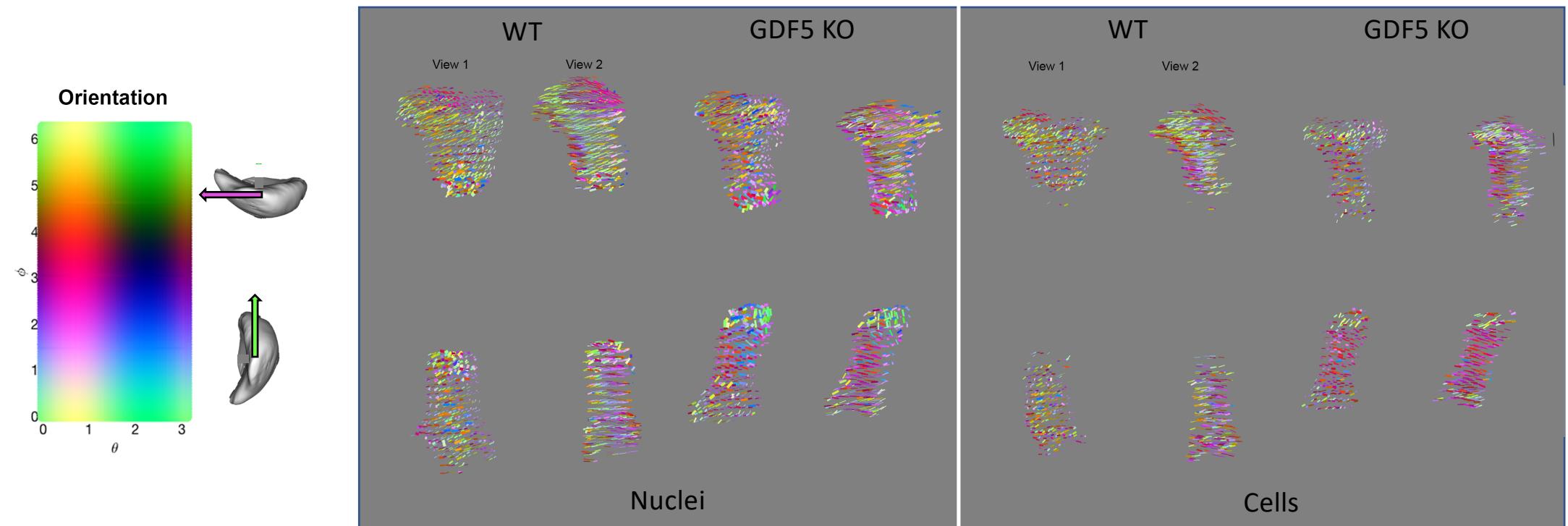
3D Maps of Morphology



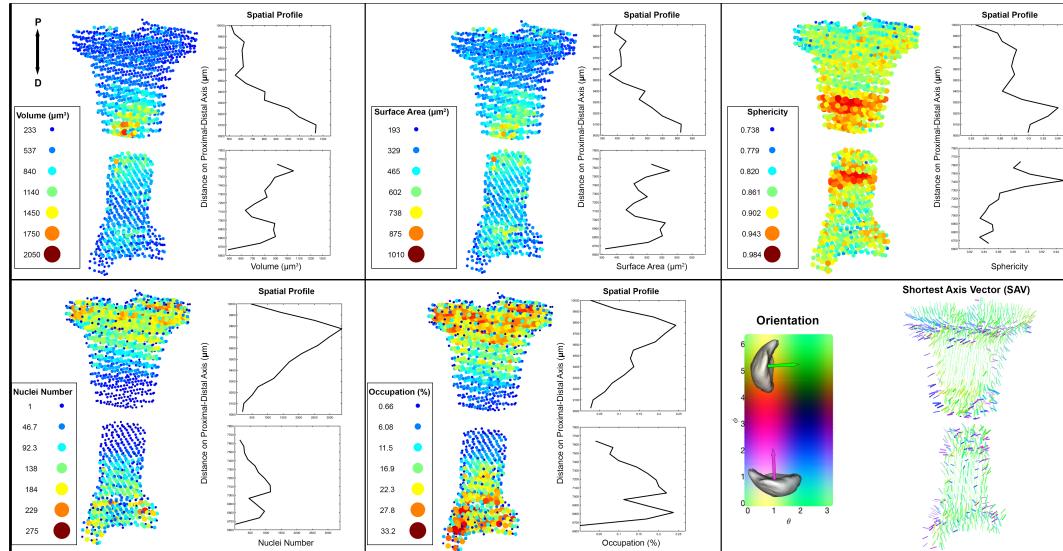
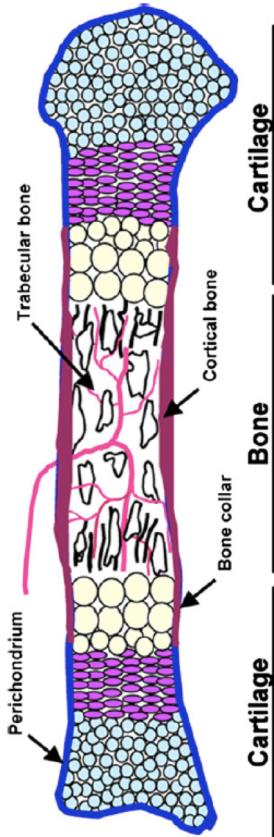
Orientation Maps – Third axis



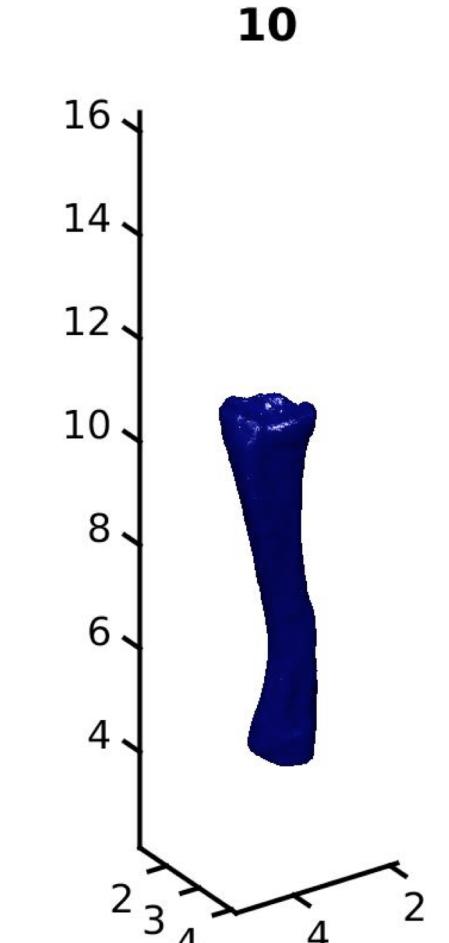
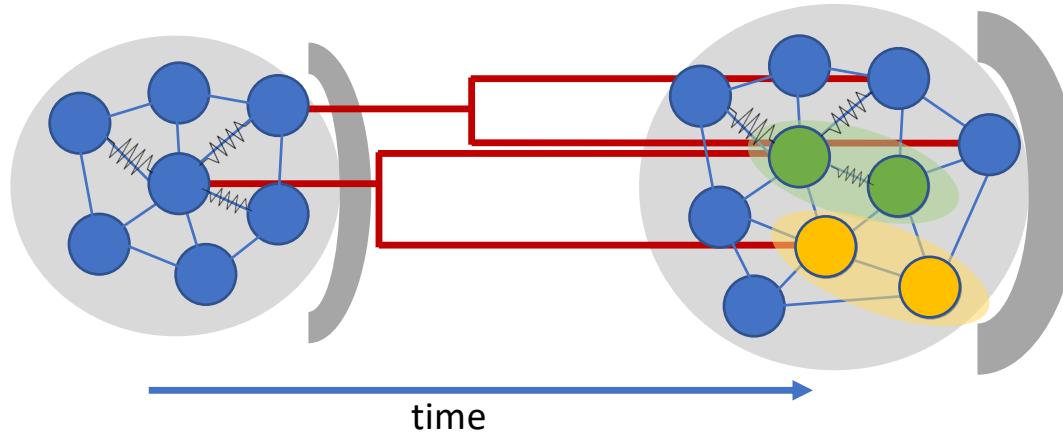
Orientation Maps – Main axis



Bone morphogenesis



Rubin, .. Villoutreix, et al., in preparation



Stern, .. Villoutreix, et al., in preparation

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Summary

Data Acquisition



Data Integration

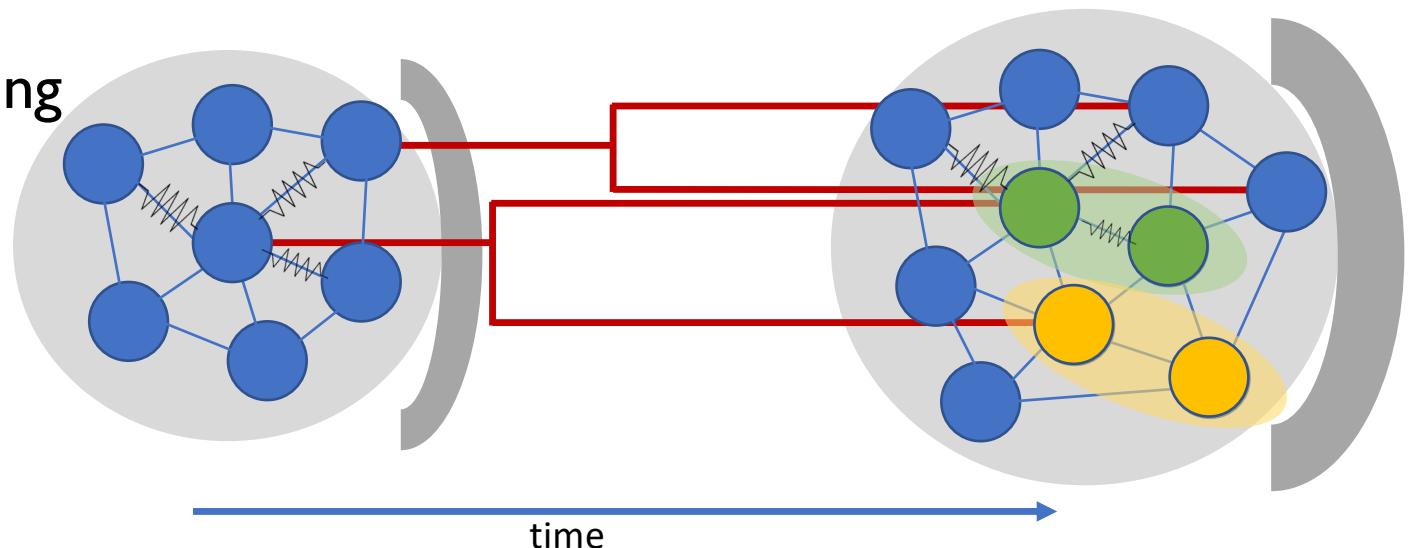


Mathematical
& Biophysical Modeling

A common methodological framework is used for studies of early development, oogenesis and bone development

A common theoretical framework is relevant to understand the interaction between cell proliferation, tissue organization and cell differentiation in a completely automated way

Large datasets need to be organized into meaningful representations





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Thank you for your attention



Nadine Peyriéras
Paul Bourgine
René Doursat
Louise Duloquin
Barbara Rizzi
Julien Delile



Stas Shvartsman
Jasmin Imran Alsous
Joakim Andén
Amit Singer
Yannis Kevrekidis



Norbert Stoop
Jörn Dunkel



Eli Zelzer
Sarah Rubin
Tomer Stern
Benny Shilo



Thomas Lecuit
Pierre-François Lenne



Frédéric Bechet
Cécile Capponi