Tissue stiffness as a coordinator for mesendoderm migration

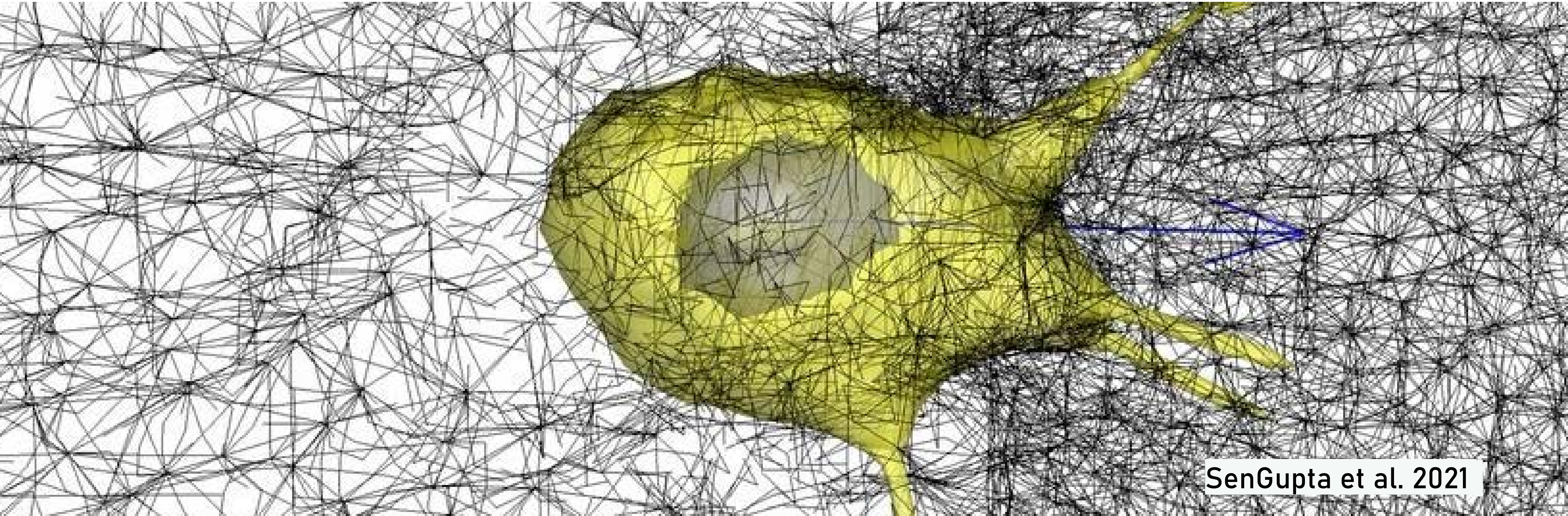
Optics, Forces, and Development Course

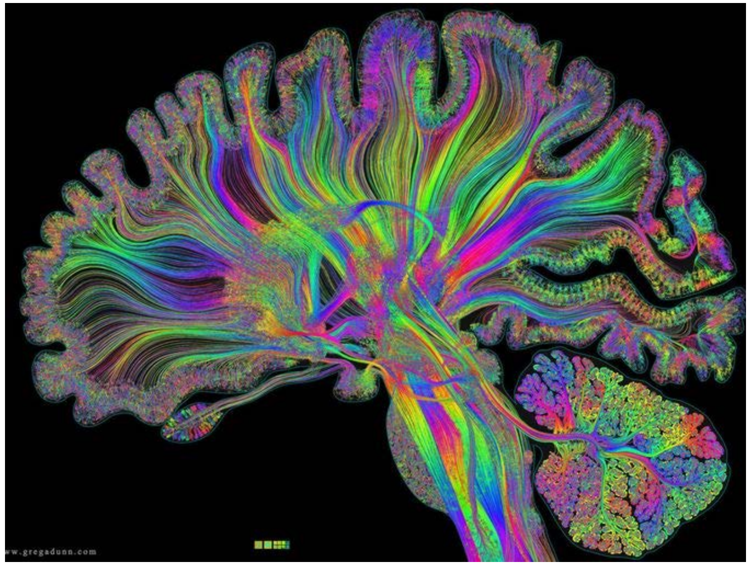
March 13, 2024

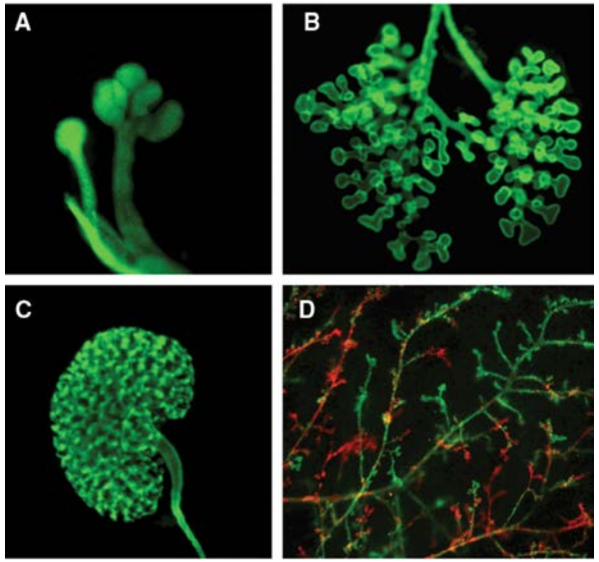
Letícia Fracaro

Mateus de Oliveira Lisboa

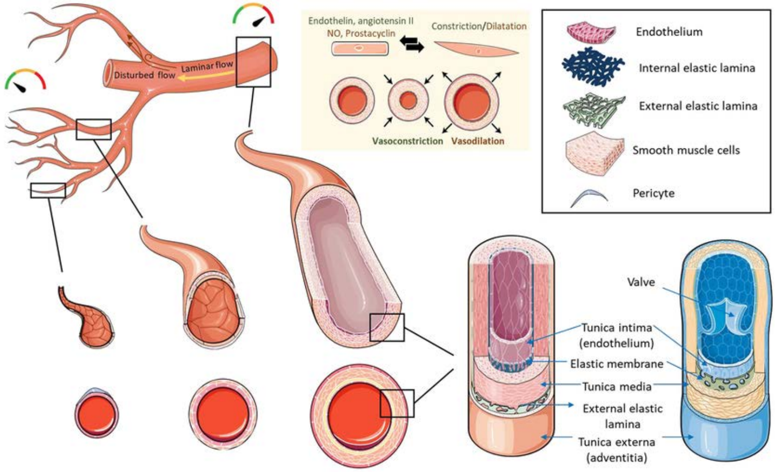
Monique Pedroza







Lu and Werb (2008) Science

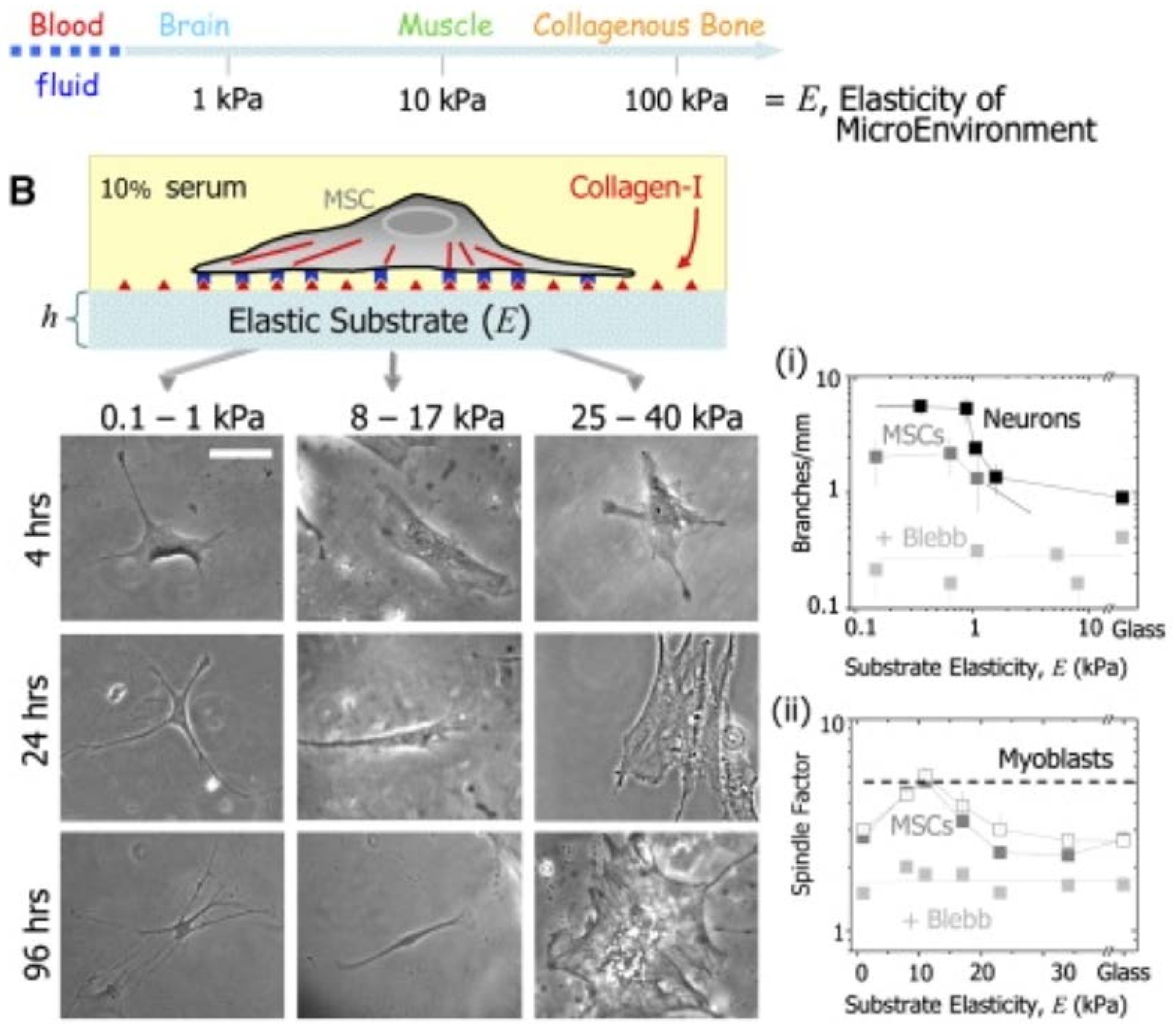


Marei et al (2022) Front. cardiovasc. med.

Tissue patterning

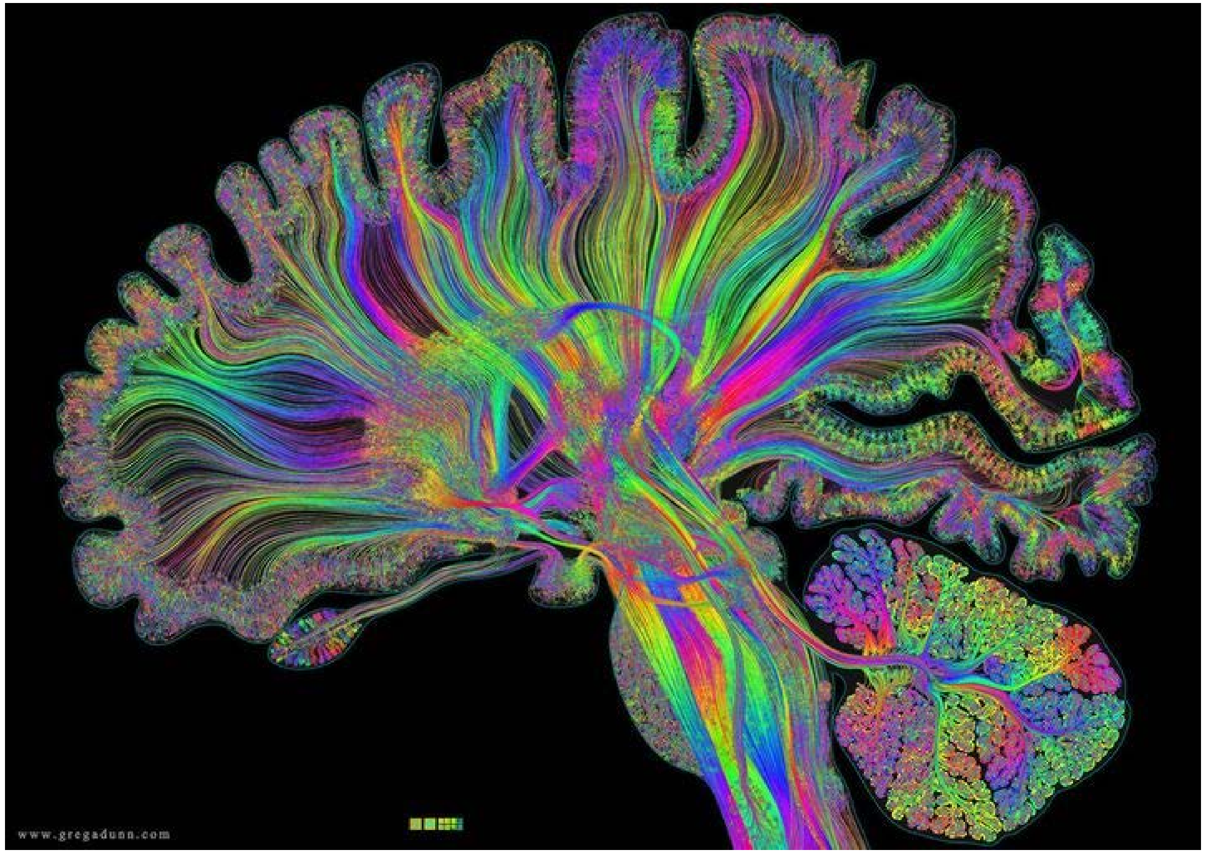
How are they formed?

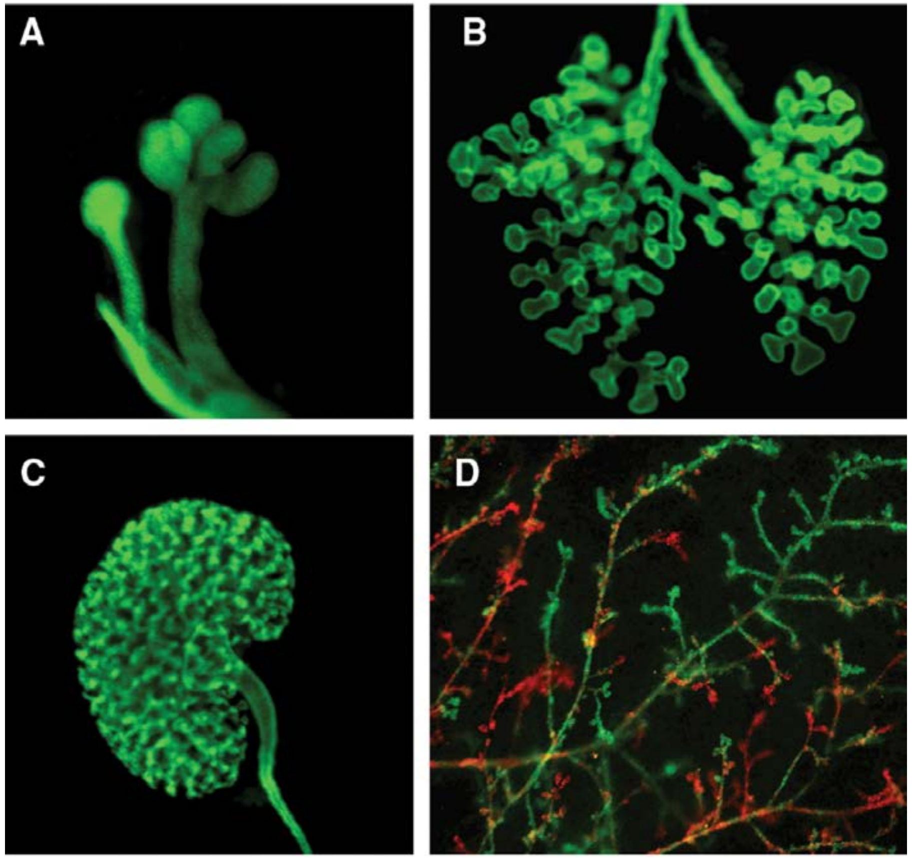
Biochemistry is not enough



Engler et al (2006) Cell 126:677-689

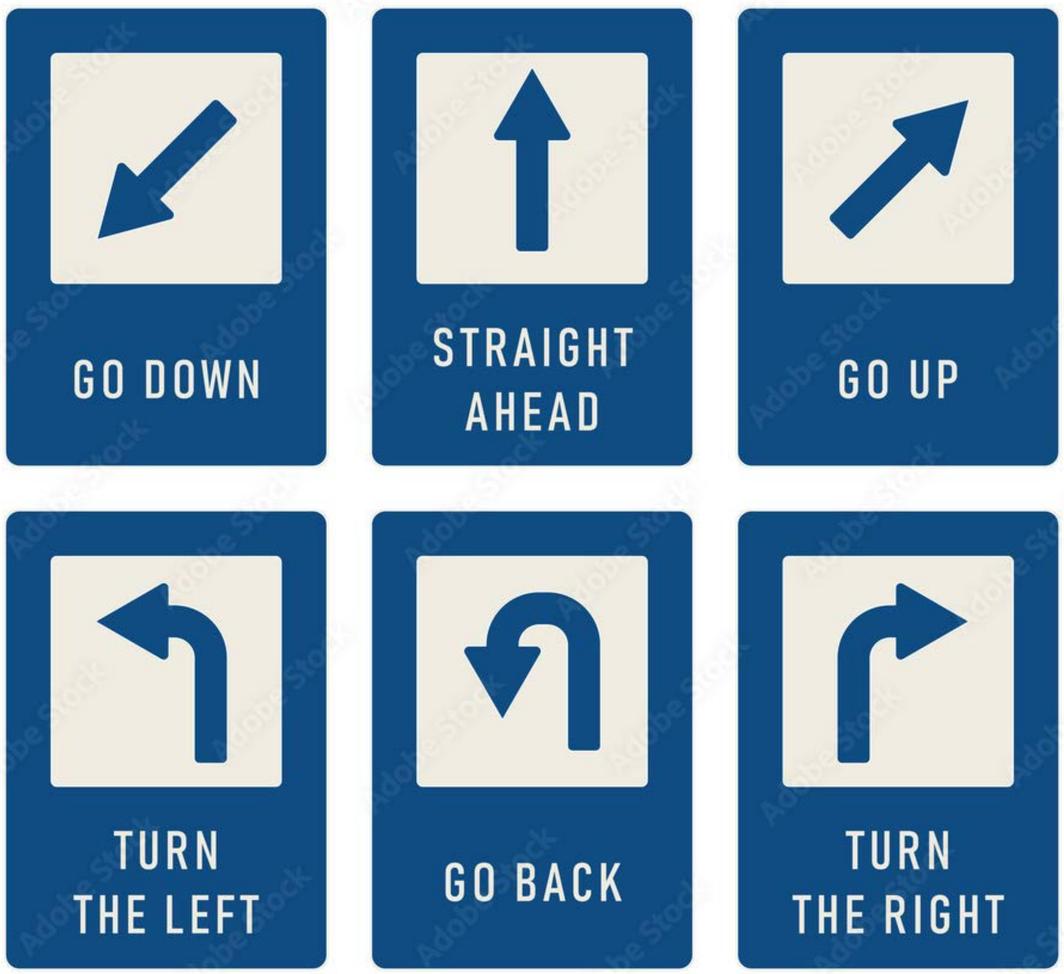
Biomechanical cues for cell shape

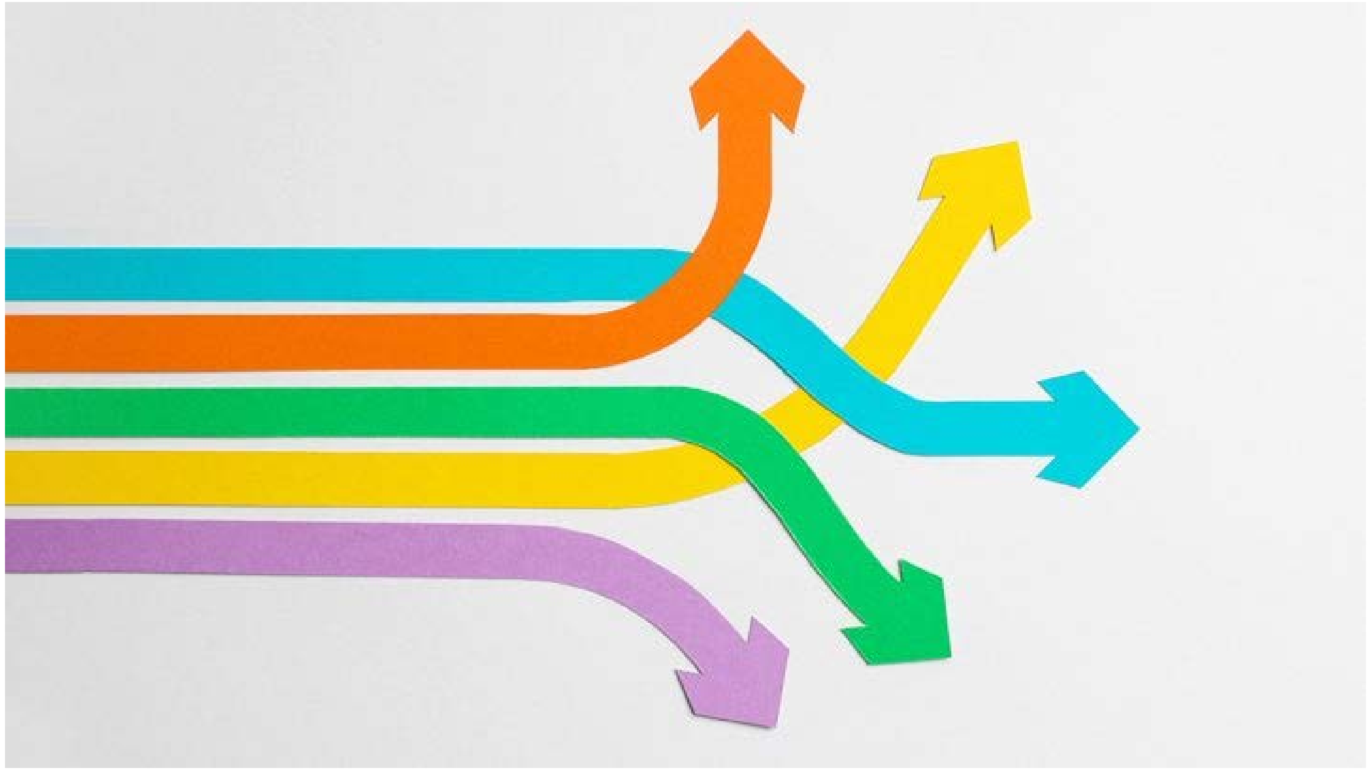




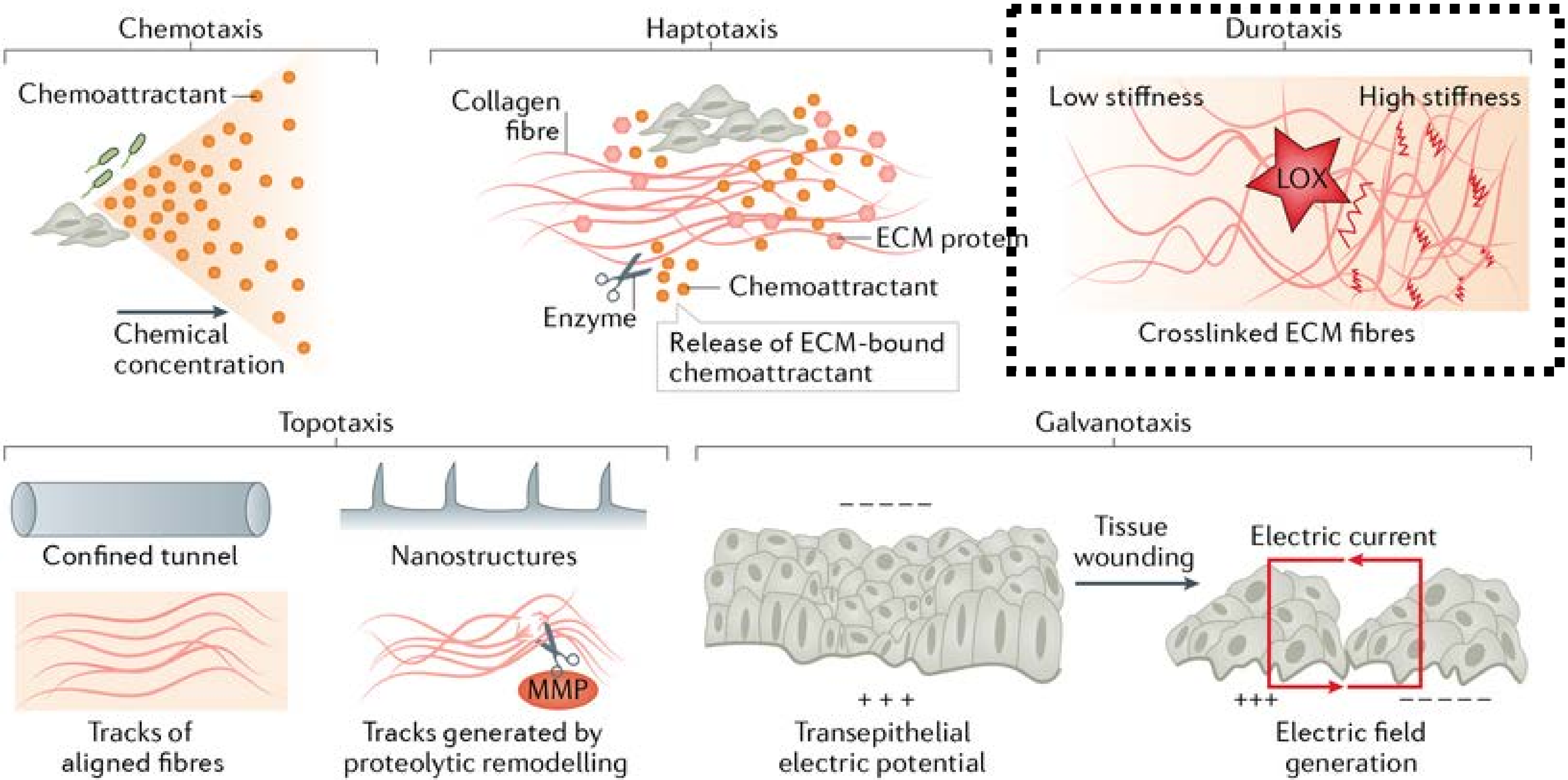
Tissue patterning

Lu and Werb (2008) Science



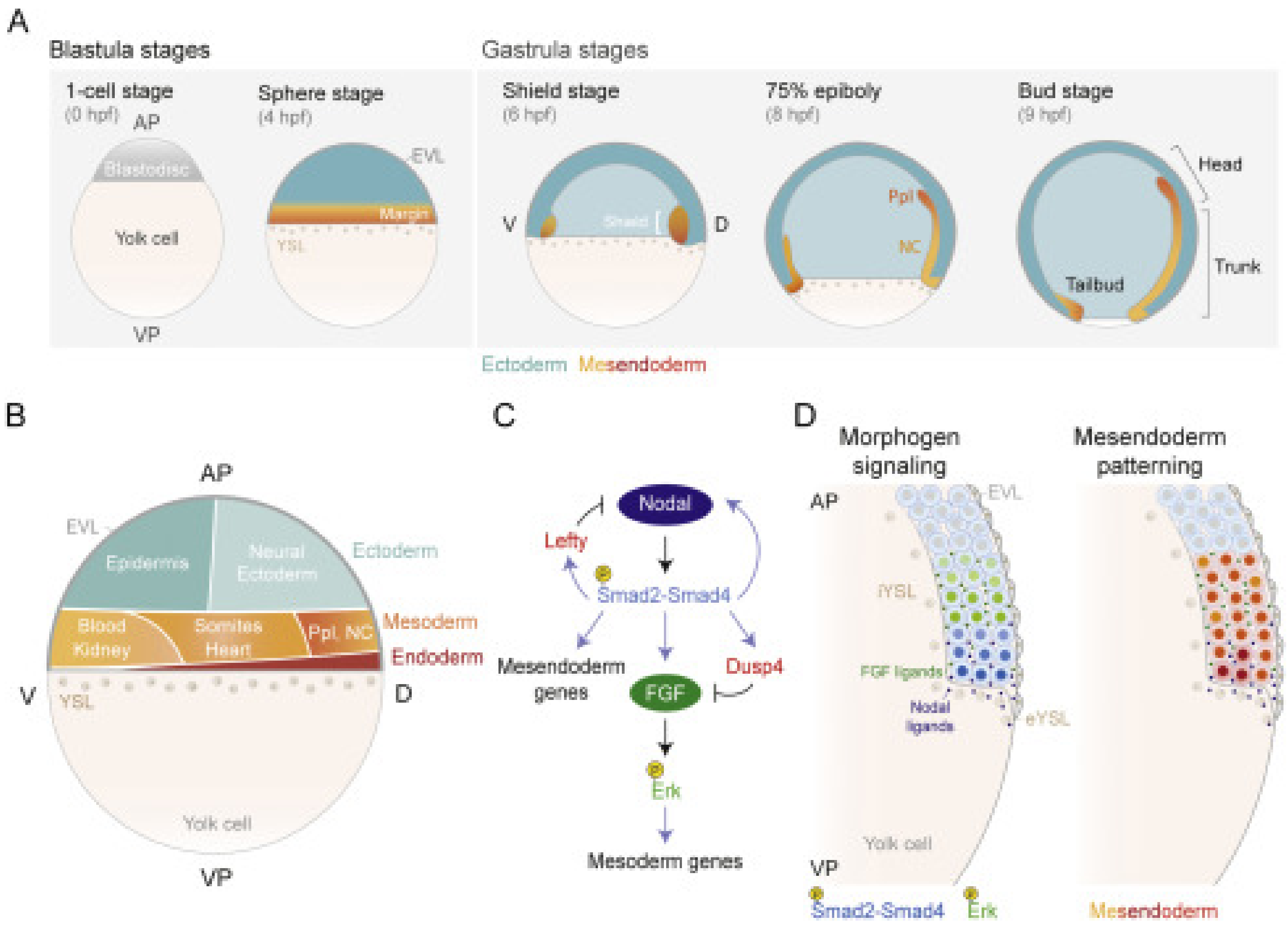


Directionality



SenGupta et al.2021

How to study tissue patterning and directionality ?



Pinheiro and Heisenberg (2020)

Gastrulation as model

Gastrulation as model

- Gastrulation is a pivotal process in early embryonic development that sets the stage for the formation of the body's three primary germ layers: the ectoderm, mesoderm, and endoderm.

- These layers subsequently give rise to all the tissues and organs of the organism.

- Studying gastrulation offers profound insights into tissue patterning and cell migration for several reasons:

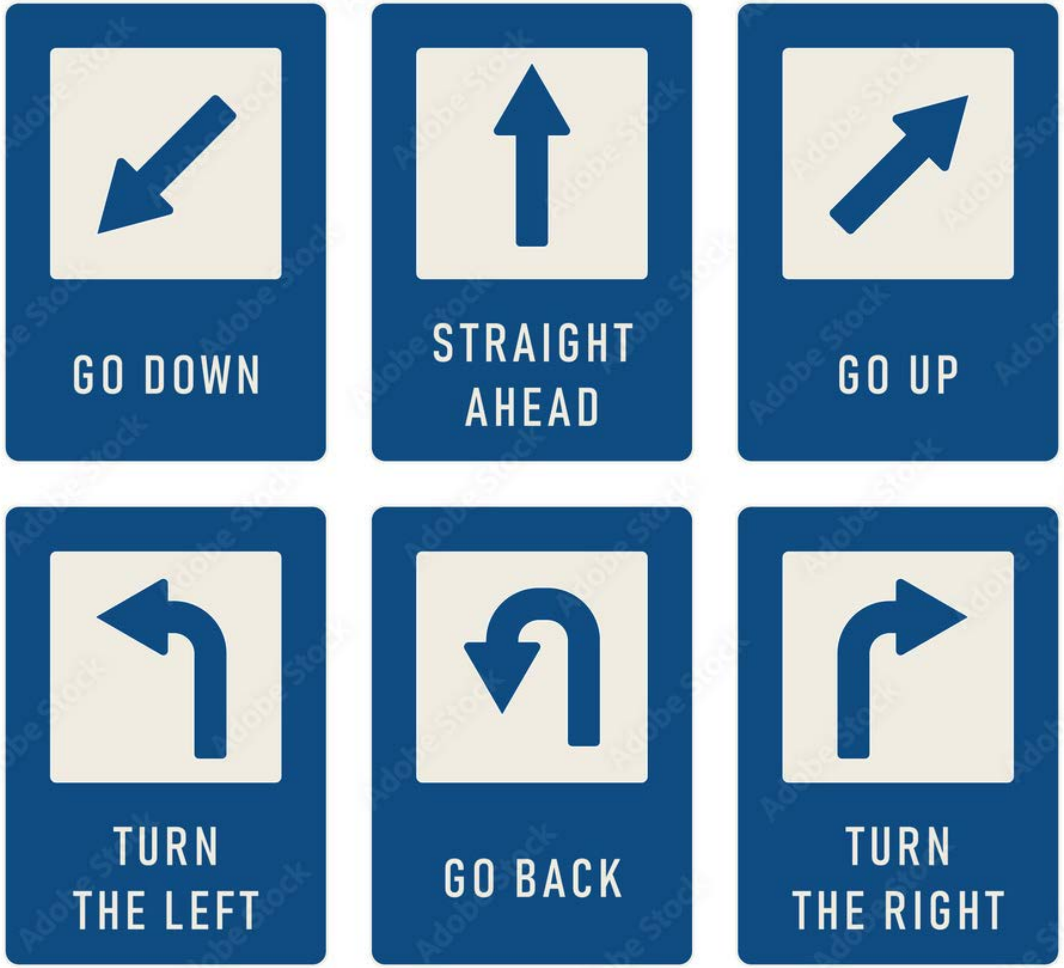
Evolutionary conserved mechanisms

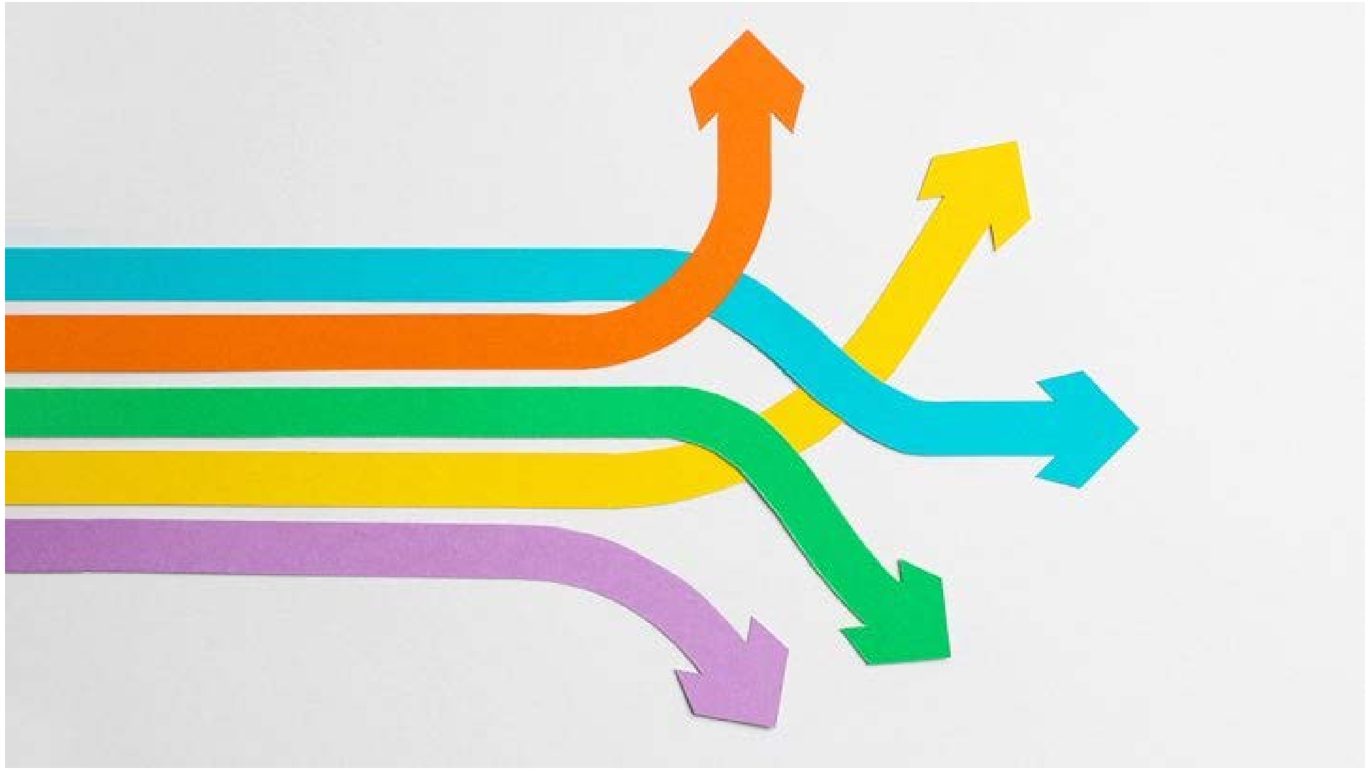
Cell Differentiation and Tissue Specification

Regulation of Gene Expression

Axis Formation and Symmetry Breaking

Interactions Between Different Cell Populations





Cell Migration and Morphogenetic Movements

nature physics

Article https://doi.org/10.1038/s41567-022-01787-6

Morphogen gradient orchestrates pattern-preserving tissue morphogenesis via motility-driven unjamming

Received: 21 March 2022

Accepted: 6 September 2022

Diana Pinheiro, Roland Kardos, Édouard Hannezo and Carl-Philipp Heisenberg

Nodal Signalling's Role

Unjamming Transition

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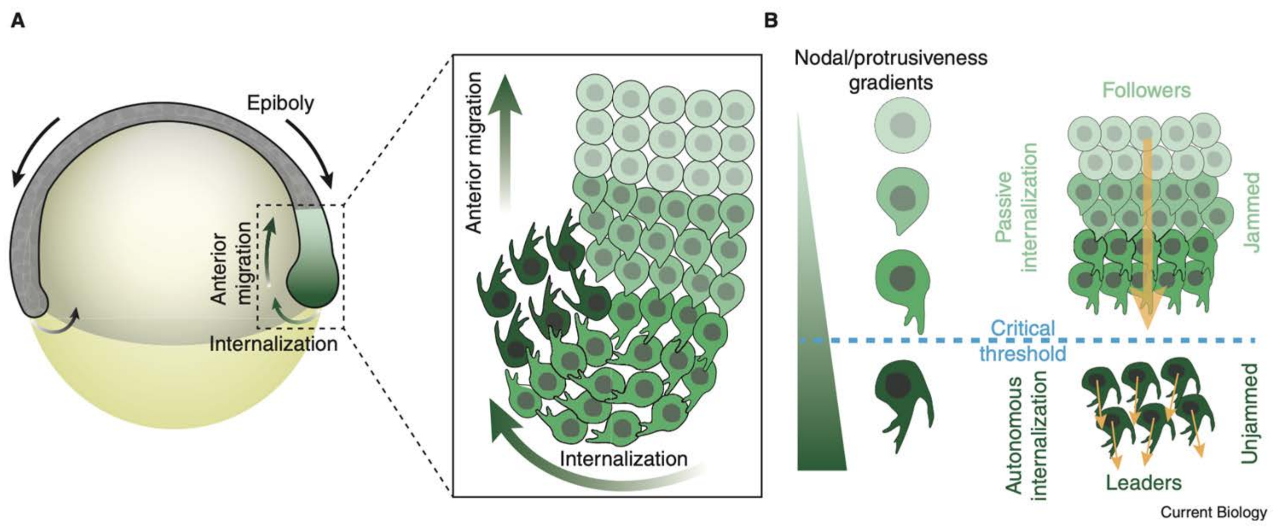
Mechanical and Biochemical Integration

Approach to understanding cellular coordination

Study - results

Nodal Signalling's Role: Demonstrates how Nodal guides mesendoderm internalization in zebrafish.



Unjamming Transition: The mechanism behind cell differentiation into leaders and followers.

Pinheiro et al 2022, Nature Physics
Morales-Navarrete and Muller, 2022 Current Biology

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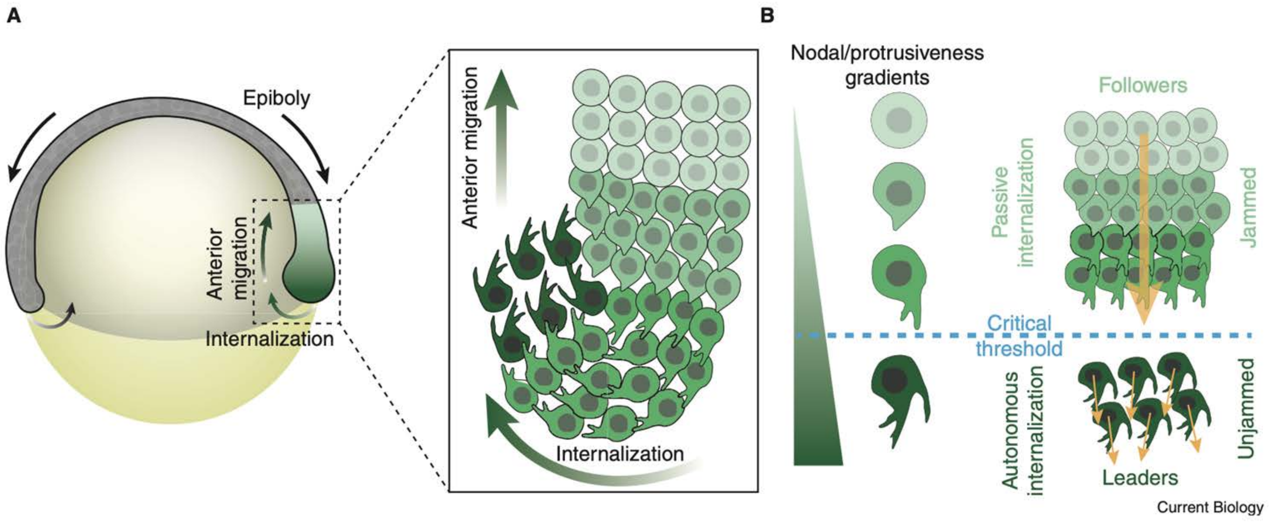

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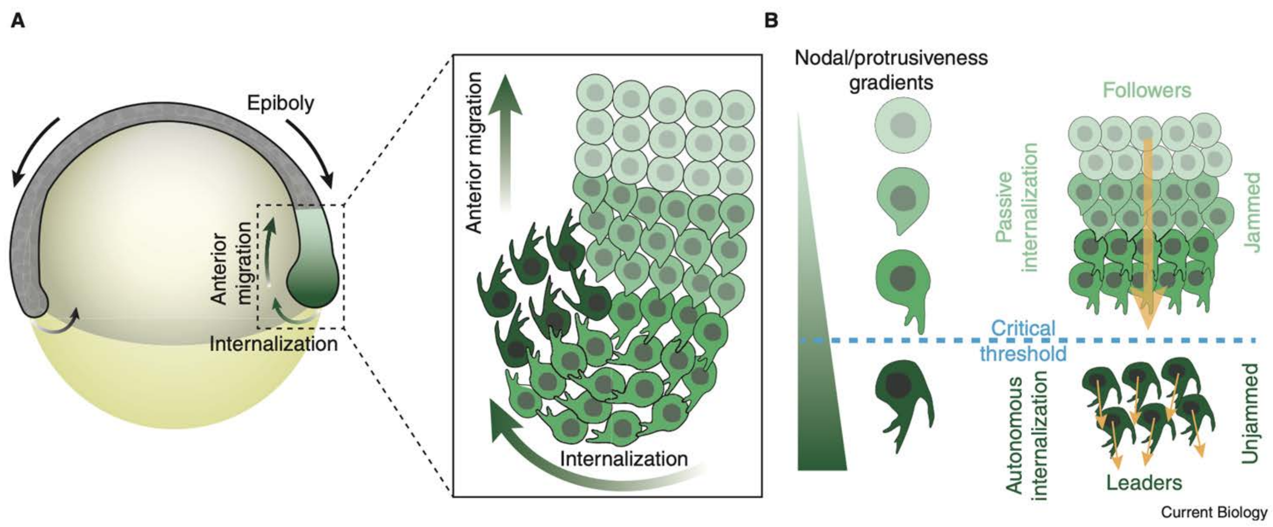
Study - results

Mechanical and Biochemical Integration: integrates mechanical forces with biochemical signaling, providing a framework for understanding the coordination between cell motility and tissue patterning in development.



Provides a new approach to understand cellular coordination and tissue mechanics during development.

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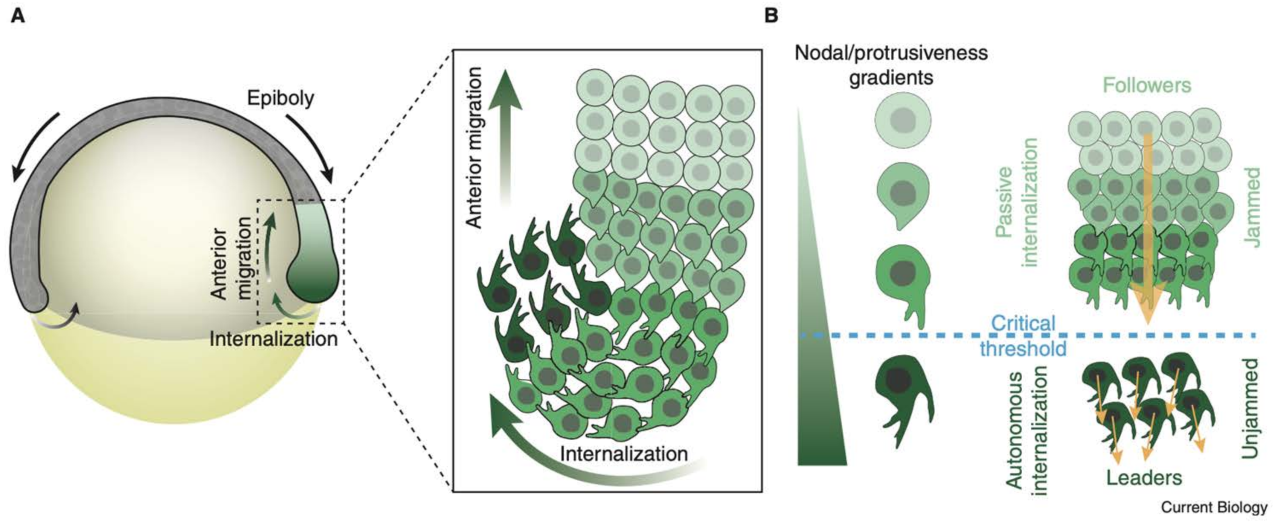

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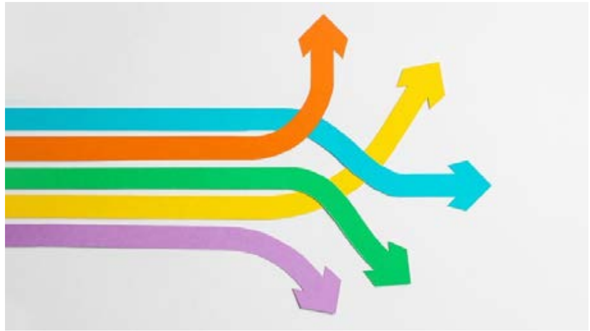
Pinheiro et al 2022, Nature Physics
Morales-Navarrete and Muller, 2022 Current Biology

Limitations and future directions

Unknown Nature of Active Forces:

- Unclear how internalization forces are generated and how cell protrusions are localized for migration.

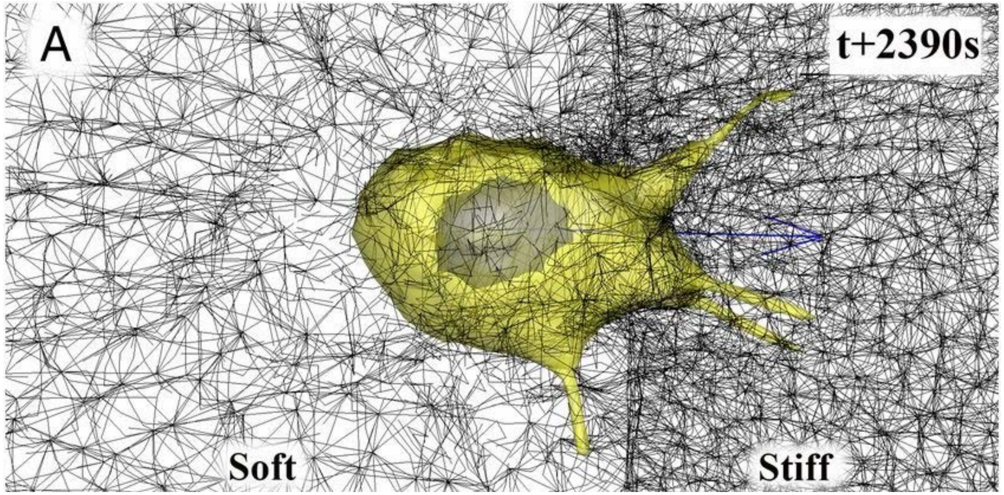


Leader Cell Direction:

- It's not explained how leader cells determine their migration direction.

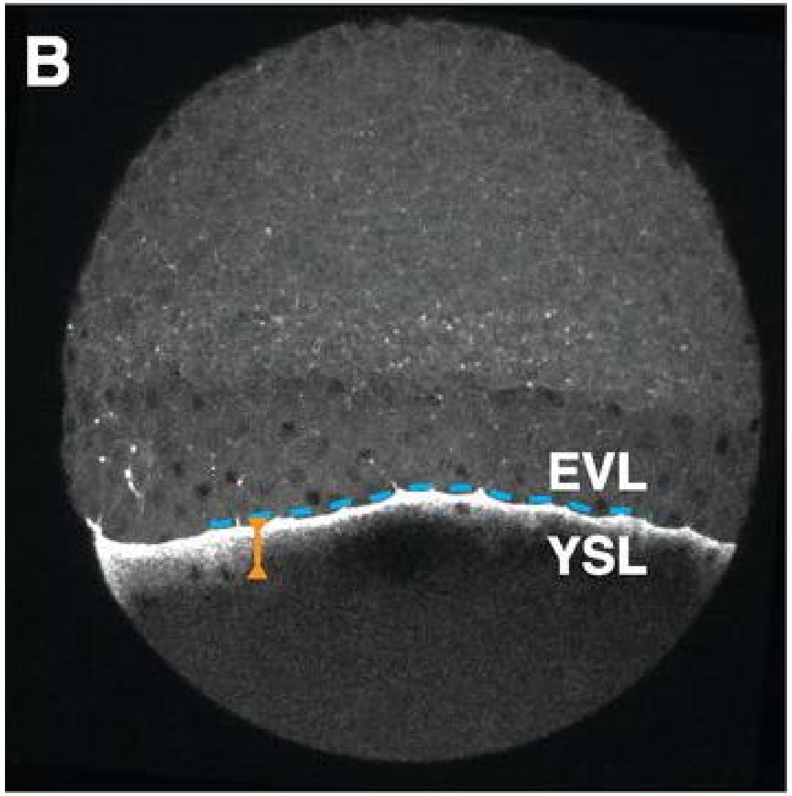
What cues guide cell migration?

Durotaxis: Directed migration via cellular response to extracellular gradient of stiffness

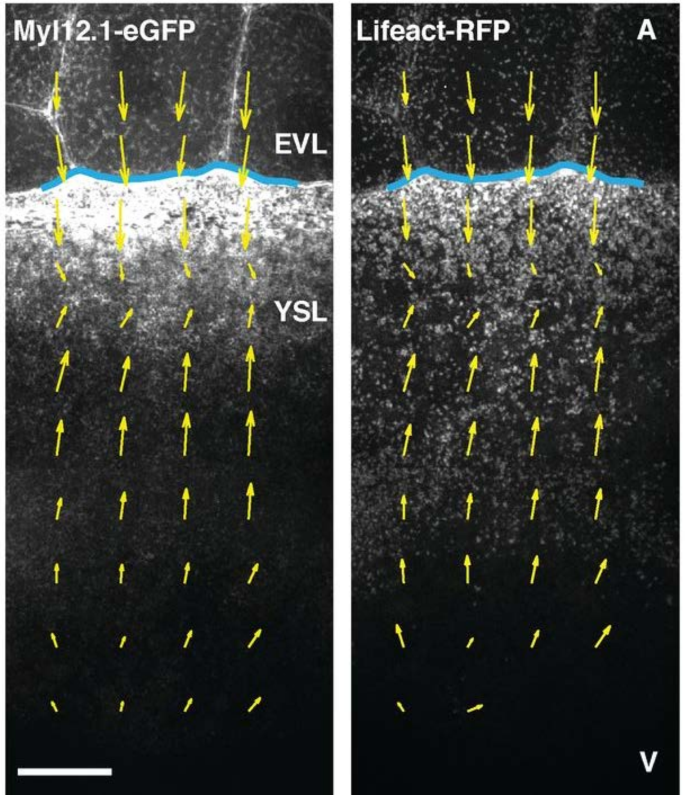


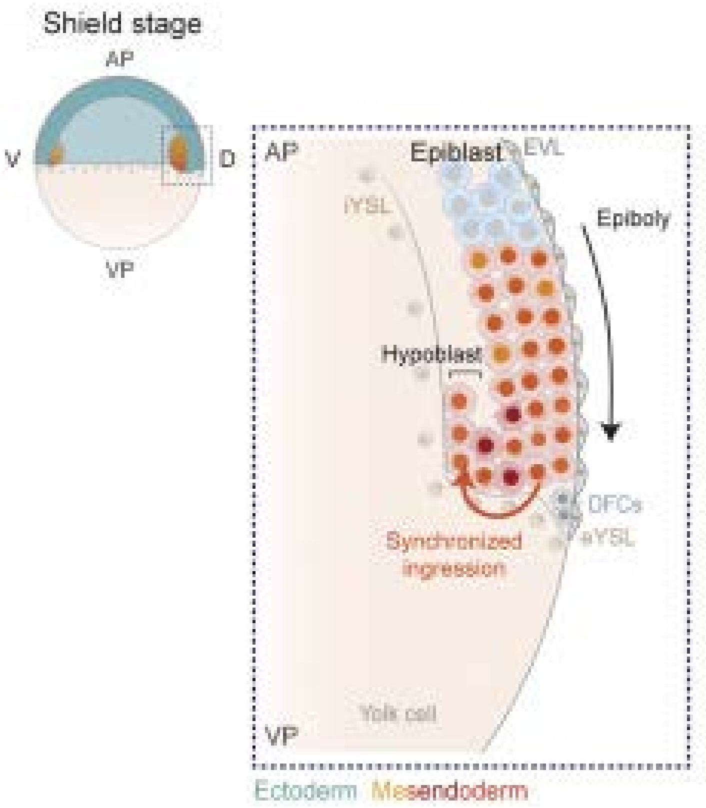
SenGupta et al. 2021 and Kim et al. 2018

Actomyosin ring is required for outer, enveloping cell layer epiboly movements



EVL - enveloping cell layer
YSL - yolk syncytial layer





Can enriched actomyosin ring also guide inner mesendoderm migration via durotaxis?

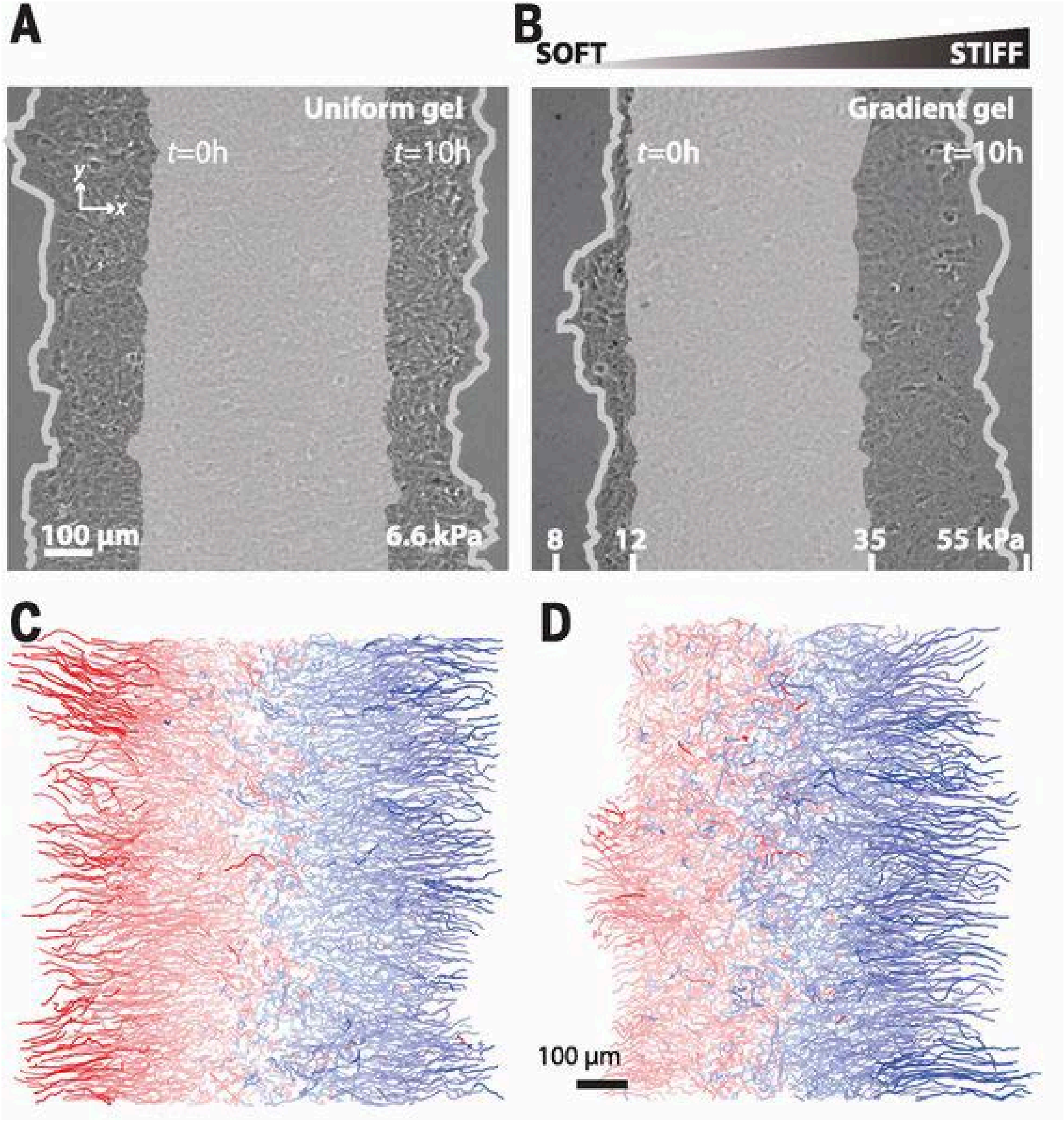
Behrndt et al. 2012

Hypothesis:

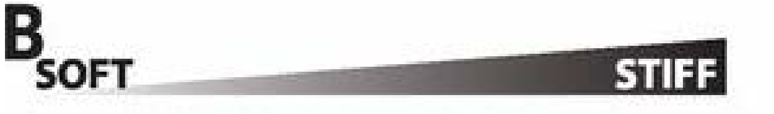
Neighboring tissue stiffness [yolk boundary] is sufficient and necessary to direct mesendoderm migration during gastrulation

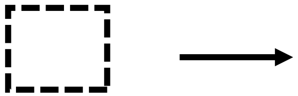
- [ ] Do mesendoderm explants migration patterns bias a stiff surface *in vitro?*

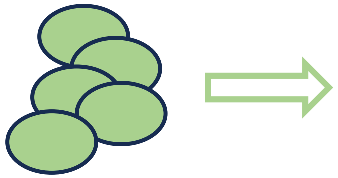
Guided mesendoderm migration via gel stiffness gradients



Sunyer et al. 2016





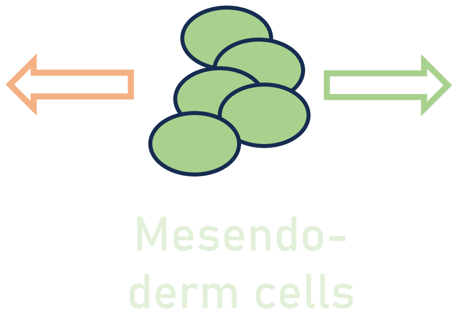


Mesendo-
derm cells

Plausible result 1:
Mesendoderm cells
migrate towards stiffer
surface

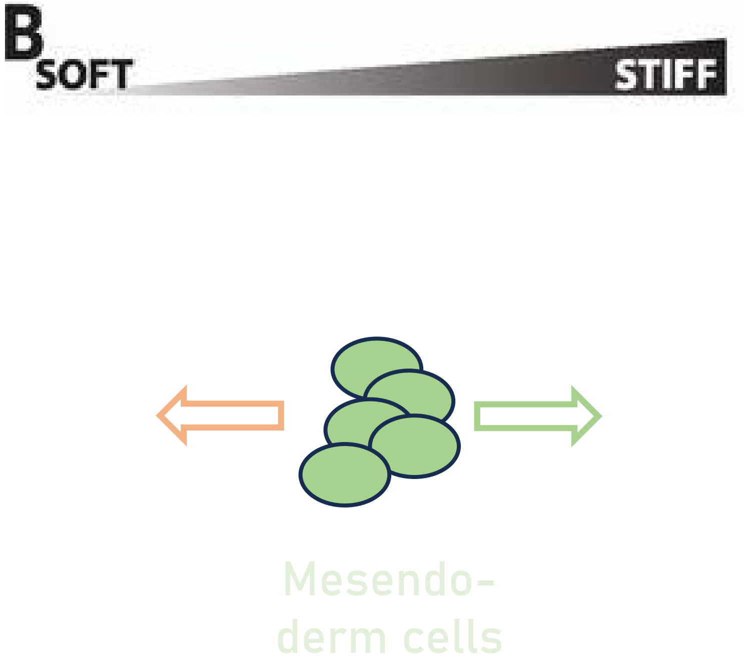
Mesendoderm

Plausible result 2:
Mesendoderm cells migrate towards softer surface



Plausible result 1:
Mesendoderm cells migrate towards stiffer surface

Plausible result 2:
Mesendoderm cells migrate towards softer surface



Plausible result 1:
Mesendoderm cells migrate towards stiffer surface

Plausible result 3:
Mesendoderm cells stay stationary or display random migration patterns

Limitations: removal of mesendoderm cells from *in vivo* mechanical and signaling environment

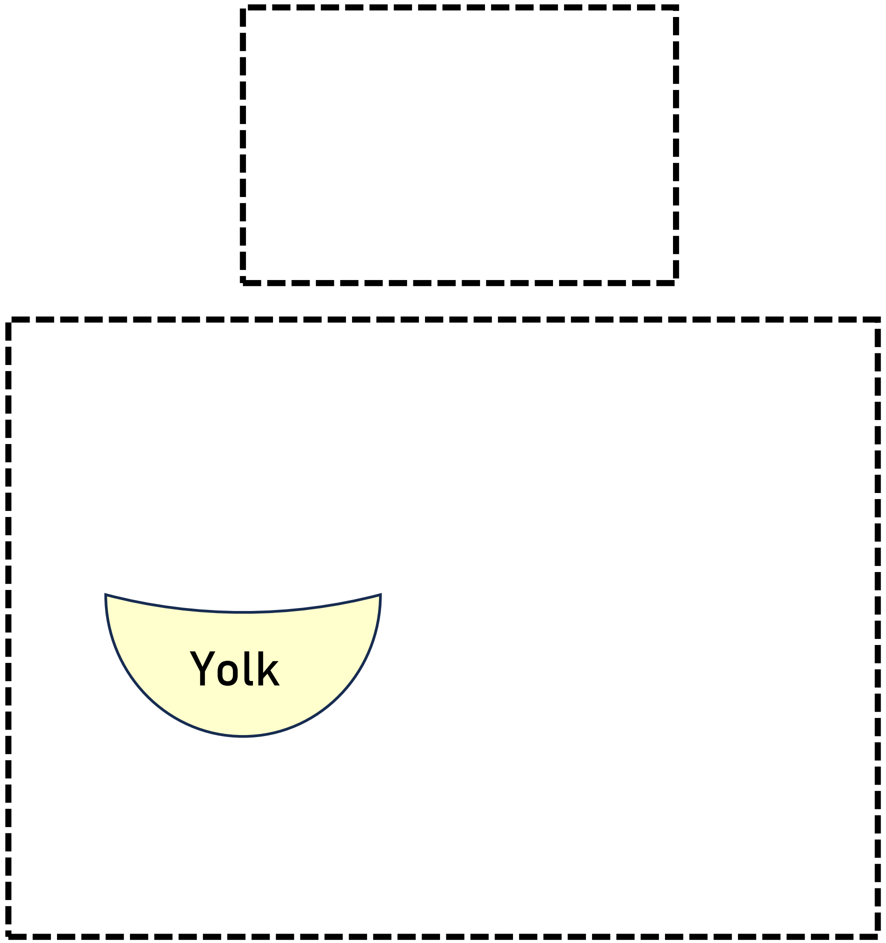
Neighboring tissue stiffness [yolk] is sufficient and necessary to direct mesendoderm migration during gastrulation

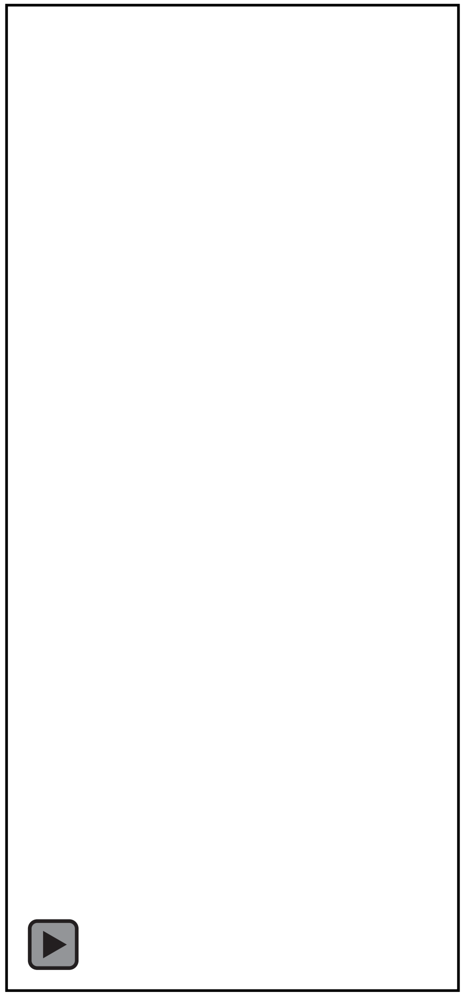
- ❑ Do mesendoderm explants migration patterns bias a stiff surface *in vitro?*

Neighboring tissue stiffness [yolk] is sufficient and necessary to direct mesendoderm migration during gastrulation

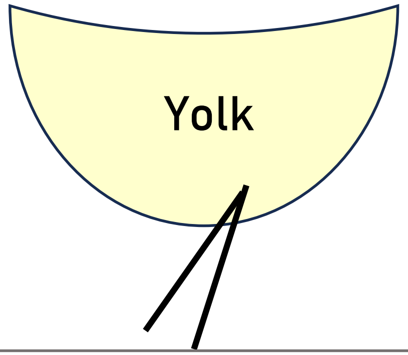
- ❑ Do mesendoderm explants migration patterns bias a stiff surface *in vitro?*
- ❑ Do mesendoderm cells migration patterns bias a stiff boundary *in vivo?*

Mesendoderm cells migrate posteriorly towards yolk, internalize and migrate anteriorly





Induce mesendoderm migration defects by release of stiffness in yolk



Miroinject translation-blocking morpholino against myosin light chain 9 (myl9-MO) or blebbistatin in yolk

→

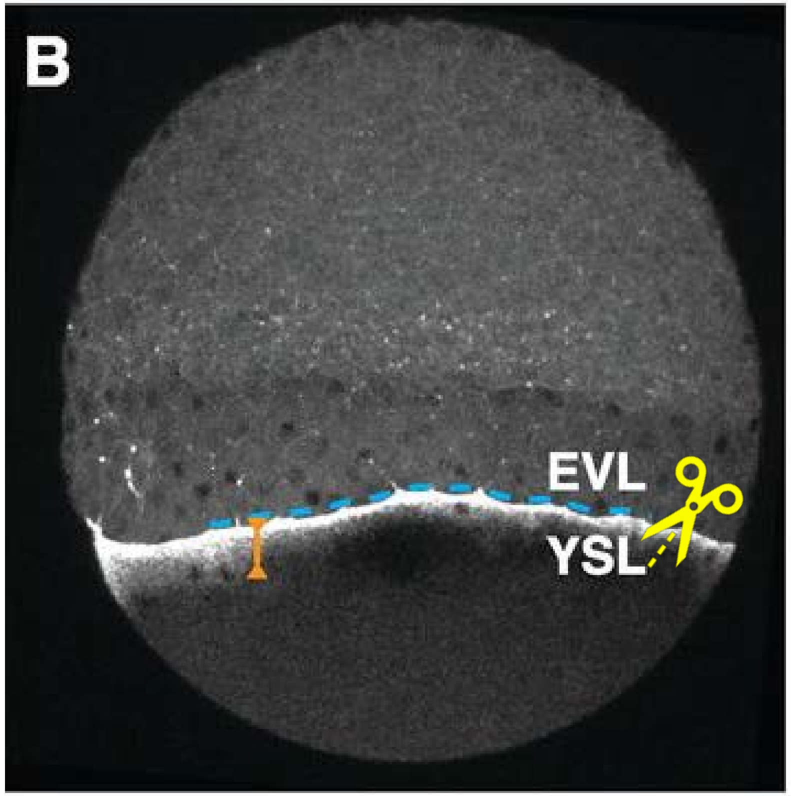
165min

Expected outcome: Mesendoderm exhibit delayed or no migration

Limitation: lack of spatial control within yolk sac

Induce mesendoderm migration defects by release of stiffness in yolk

Ablate actomyosin ring at pre-migration site of mesendoderm



EVL - enveloping cell layer
YSL - yolk syncytial layer

Expected result for control –
no defects in mesendoderm migration

Expected result for ablated embryos –
Mesendoderm exhibit delayed or no migration

165min

Behrndt et al. 2012

Rescue mesendoderm migration by localized stiff stiffness induction at dorsal yolk boundary

Localized induced contractility or compression via:

- ❑ optogenetics [Rac1]
- ❑ *in vivo* atomic force microscopy

Expected outcome:

Rescue of directed mesendoderm migration

Neighboring tissue stiffness [yolk] is sufficient and necessary to direct mesendoderm migration during gastrulation

- ❑ Do mesendoderm explants migration patterns bias a stiff surface *in vitro?*
- ❑ Do mesendoderm cells migration patterns bias a stiff boundary *in vivo?*

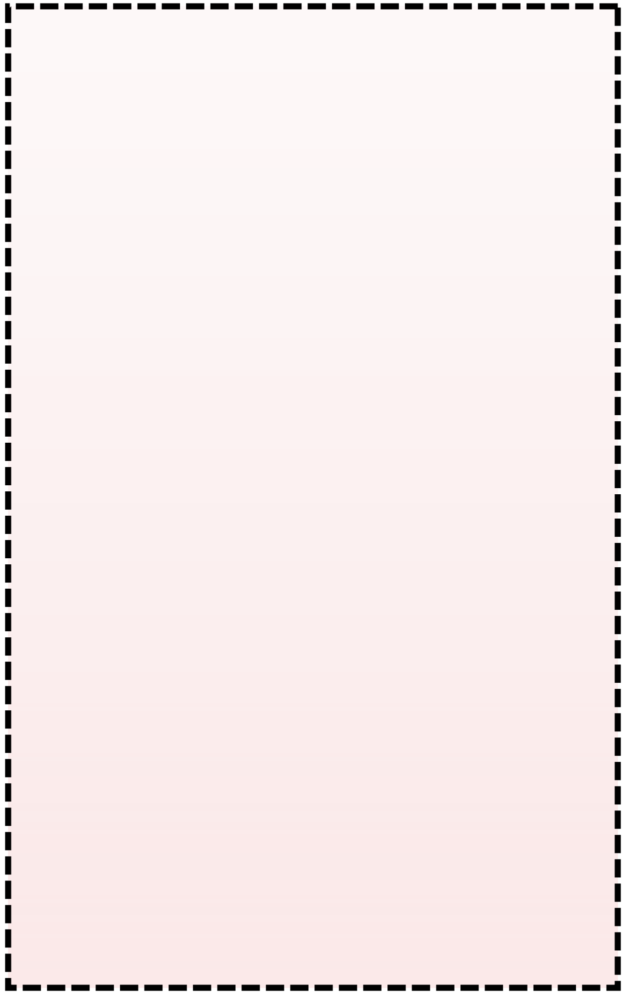
Neighboring tissue stiffness [yolk] is sufficient and necessary to direct mesendoderm migration during gastrulation

- ❑ Do mesendoderm explants migration patterns bias a stiff surface *in vitro?*
- ❑ Do mesendoderm cells migration patterns bias a stiff boundary *in vivo?*
- ❑ Is localized tissue stiffness sufficient to redirect mesendoderm migration patterns *in silico?*

Validate and predict mesendoderm migration directionality *in silico*

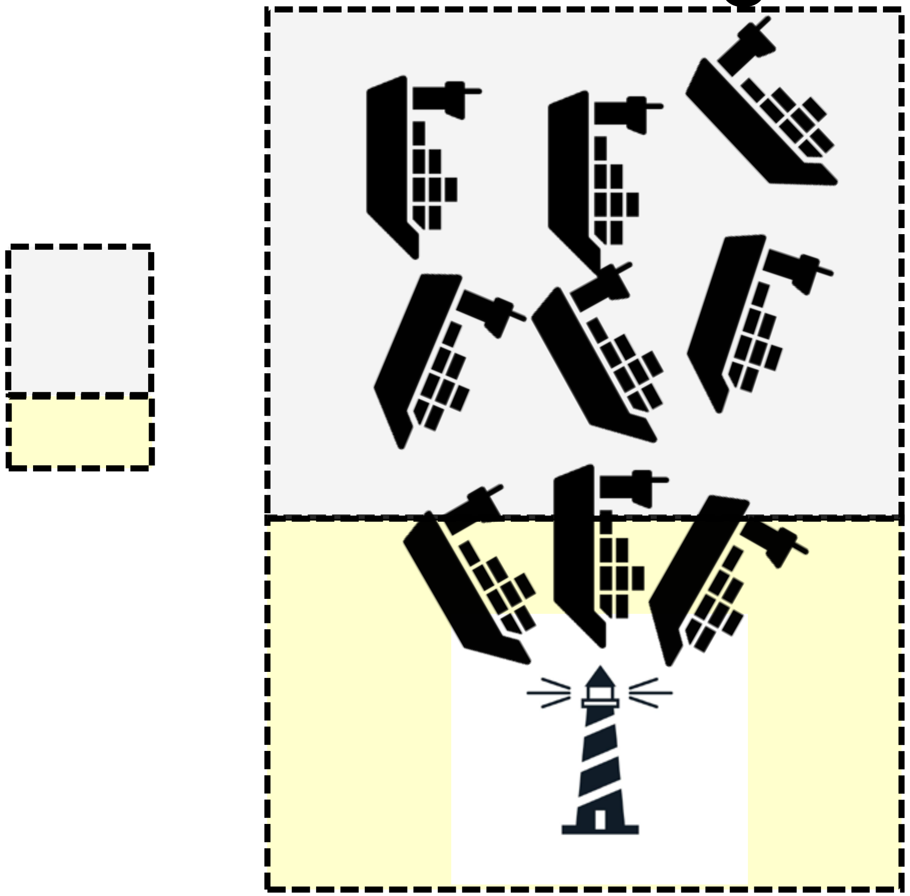
Validation of initial mesendoderm migration

Stiffness gradient



Prediction of subsequent mesendoderm directionality

Localized stiffness as a spatially and temporal director for mesendoderm migration



Group of boats [mesendoderm] passively ride a wide current [epiboly]

Lighthouse [stiffness boundary] in sight gives directionality to boats [mesendoderm]

- ❑ Proper tissue patterning requires mechanical cues.
- ❑ These mechanical cues manifest at both large tissue scales such as epiboly and timely, precise scale movements such as regionalized stiffness
- ❑ Important factor to consider with new emerging field of stem cell modeling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Thank you!!!

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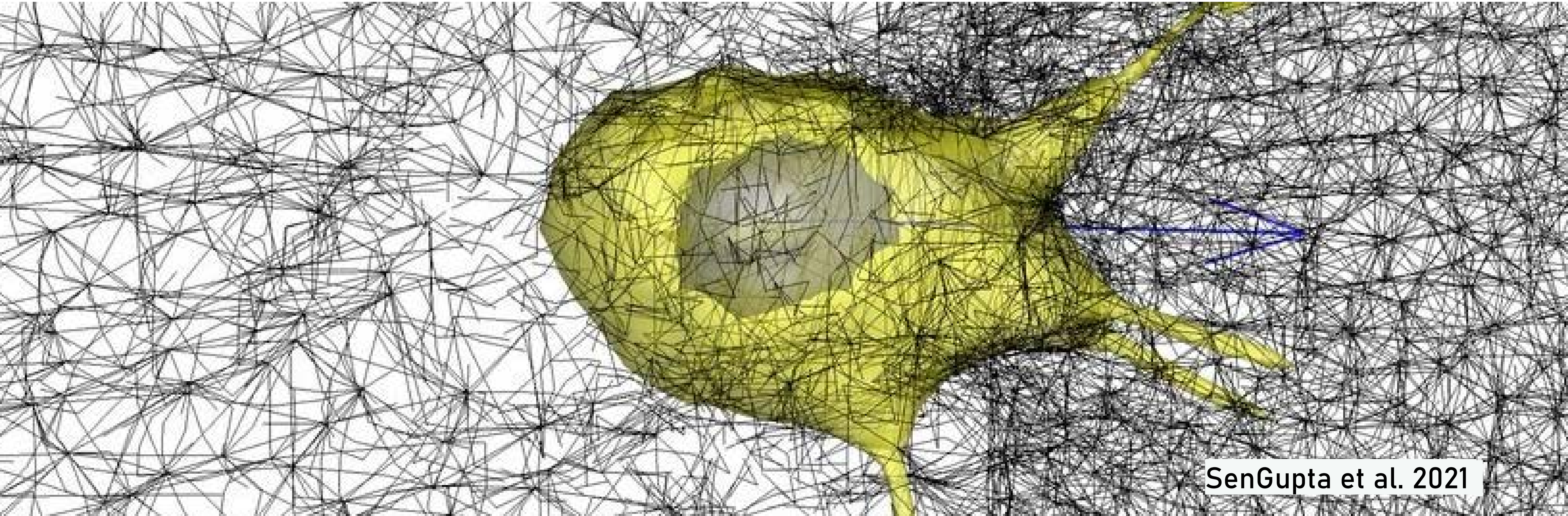

SenGupta et al. 2021