

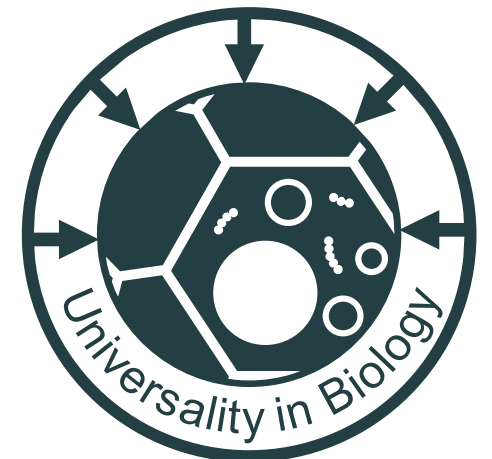
MIT Biophysics Seminar Series
8 April 2026

From Symmetry Breaking to Cellular Geometry: Physical Principles of Heart Patterning

Chiu Fan Lee

Department of Bioengineering, Imperial College London, UK

IMPERIAL





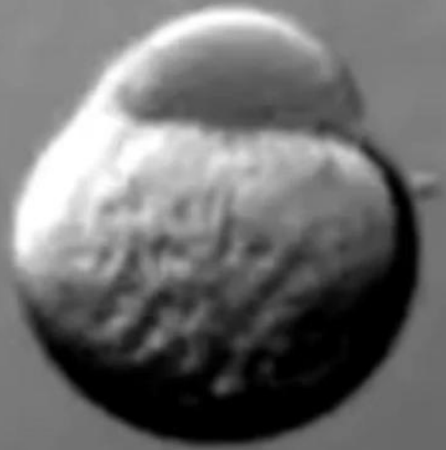
Zebrafish Embryonic Development (1-cell stage to 85 hpf)

Swinburne IA, Mosaliganti KR, Green AA, Megason SG.
PLoS One. 2015 Aug 5;10(8):e0134005
PMID: 26244658

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- Dorsal-ventral symmetry breaks first
- Anterior-posterior symmetry breaks at ~5 hours post fertilisation (hpf)
- Left-right symmetry breaks at ~11 hpf



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First story: Left–right determination at 11–12 hours post fertilisation (hpf), culminating in leftward heart jogging at 24 hpf

Second story: Endocardial cell patterning in the beating heart at ~48 hpf

Acknowledgement



Julien Vermot



Sulaimaan Lim

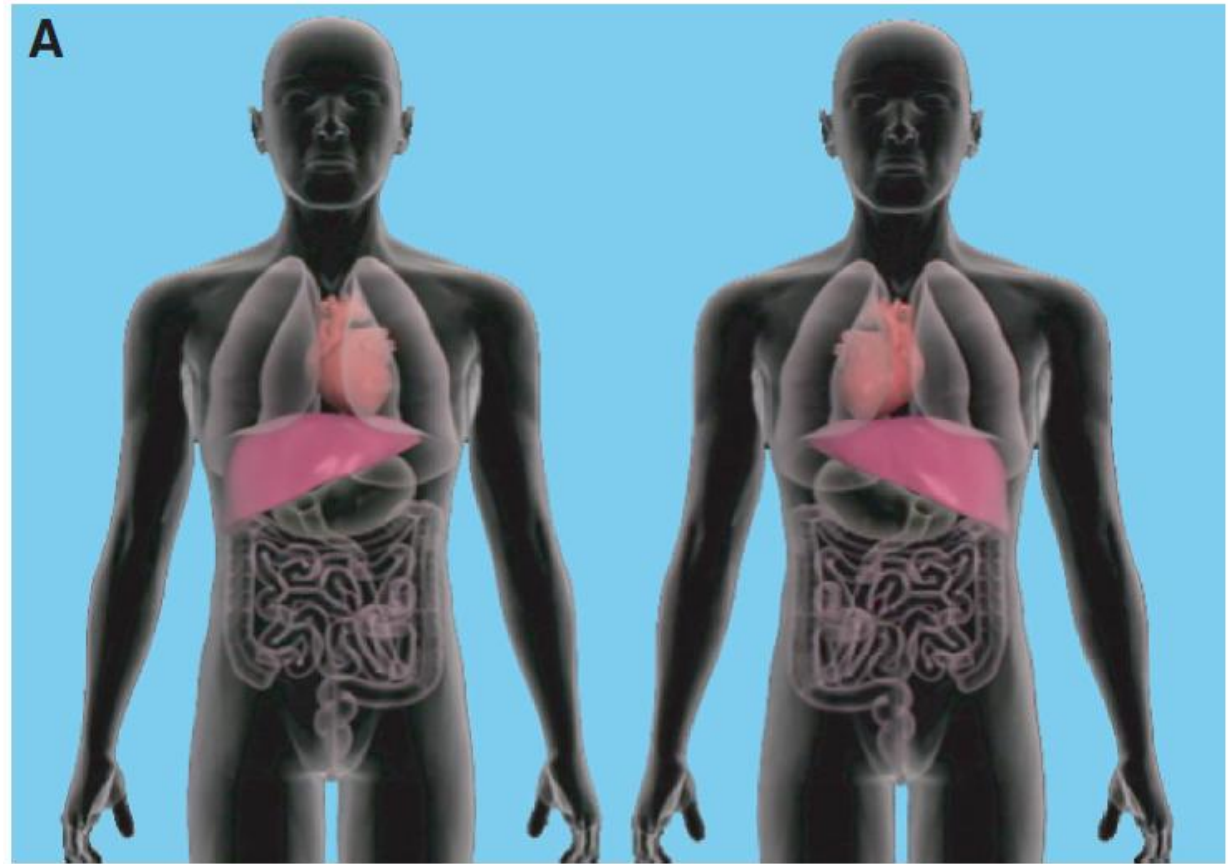


Anil Bharath



Antoine Sanchez





Hirokawa, Tanaka, Okada (2009) Cold Spring Harb Perspect Biol

Story 1: Left right asymmetry determination

How does the body know left from right?

A bit of history

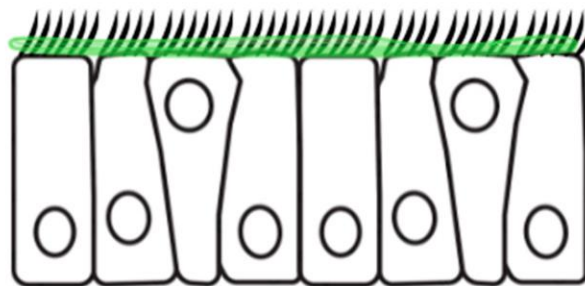
- **1904–1930s:** situs inversus documented clinically

How does the body know left from right?

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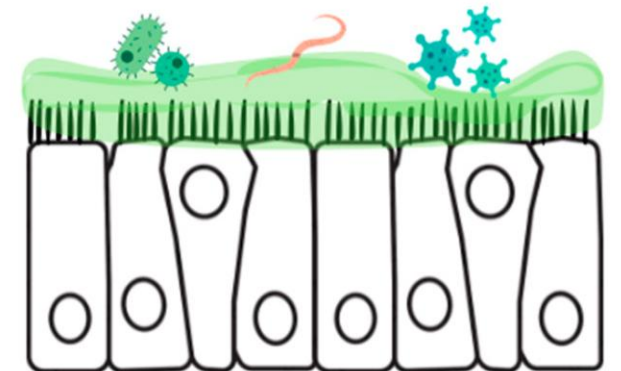
- **1904–1930s:** situs inversus documented clinically
- **1970s:** patients with immotile cilia syndrome were found to have ~50% situs inversus

Coordinated ciliary movement transports mucus and impurities towards the throat, facilitating airway clearance.



Normal cilia

Lack of movement of epithelial cilia contributes to mucus thickening and accumulation of contaminants and pathogens in the respiratory tract, inducing infections.



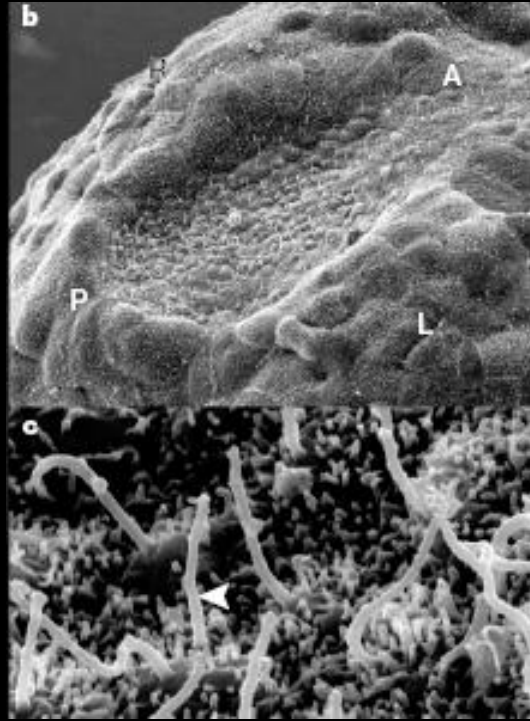
Faulty cilia (PCD)

How does the body know left from right?

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- **1998:** Discovery of nodal flow in mouse embryos [Nonaka et al (1998) Cell]

Mouse node

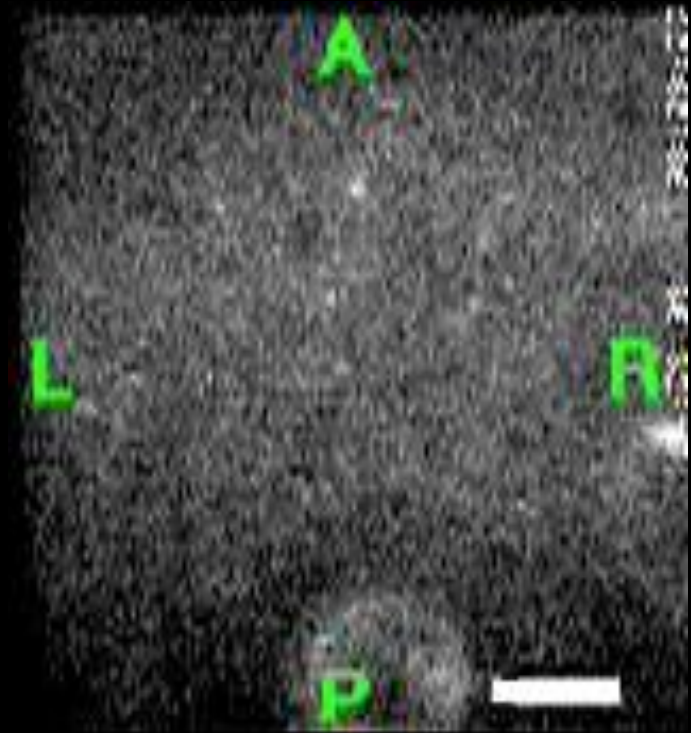


Hamada, 2003

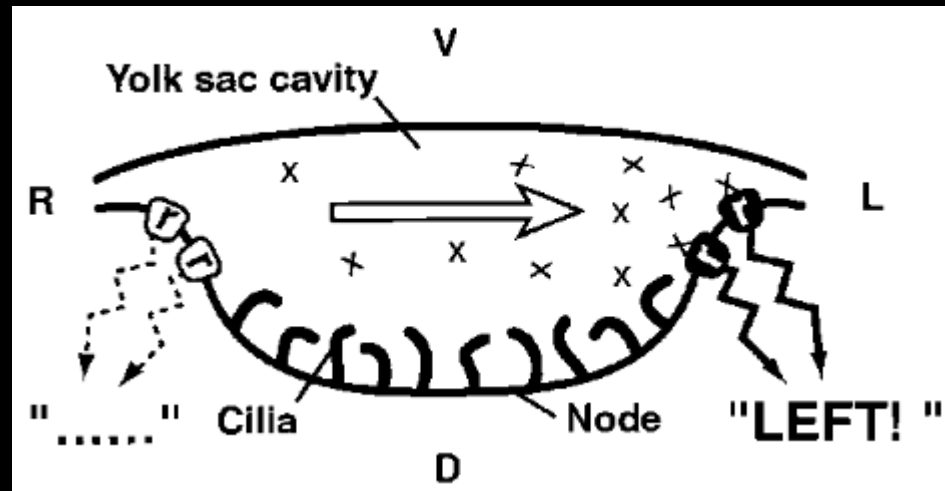
Beating cilia



5 mm



Nonaka et al. Cell, 1998



How do rotating cilia lead to directional flow?



Cartwright, Piro & Tuval (2004) PNAS

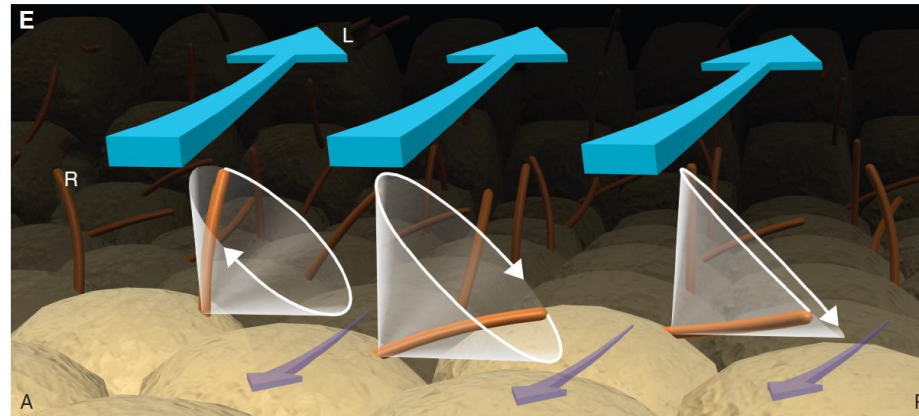


Illustration in Hirokawa, Tanaka, Okada (2009) Cold Spring Harb Perspect Biol

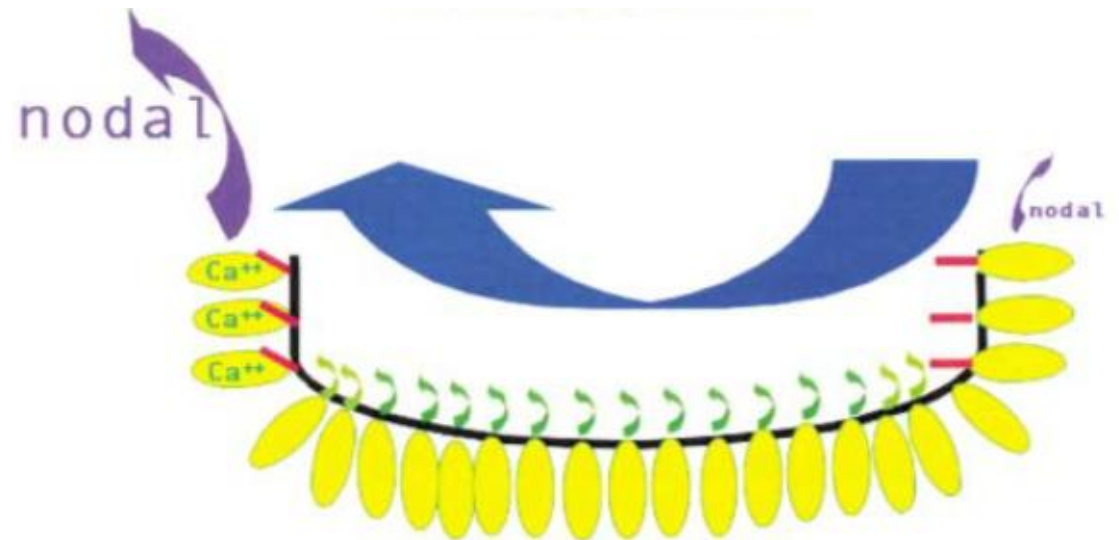


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- **2000s:** Mechanosensing model

[Tabin & Vogan (2003) Genes & Dev, McGrath et al (2003) Cell]

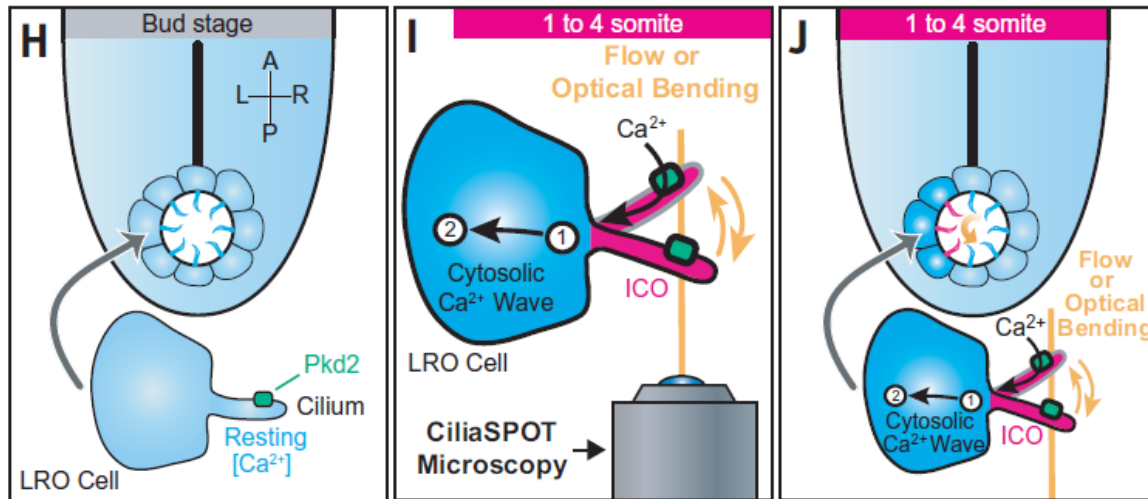


Sufficiency of sensory cilia for LR determination

Cilia function as calcium-mediated mechanosensors that instruct left-right asymmetry

Lydia Djenoune^{1†}, Mohammed Mahamdeh^{1†}, Thai V. Truong², Christopher T. Nguyen^{1,3,4}, Scott E. Fraser², Martina Brueckner⁵, Jonathon Howard⁶, Shiaulou Yuan^{1*}

Mouse

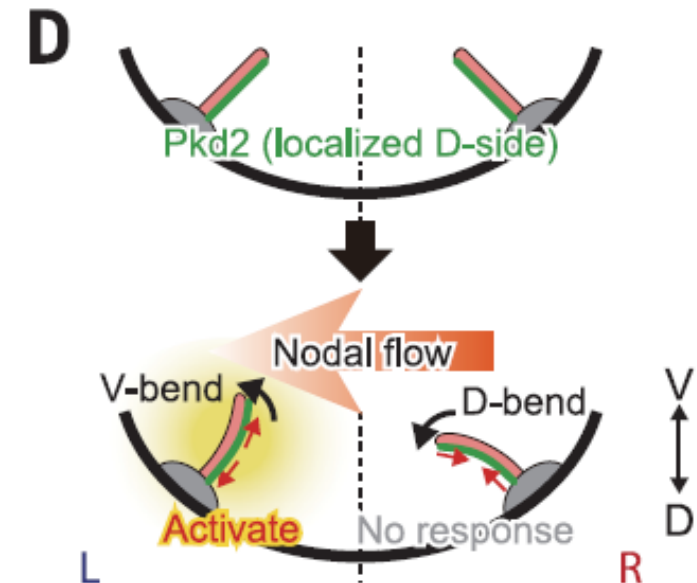


Djenoune *et al.*, *Science* **379**, 71–78 (2023)

Immotile cilia mechanically sense the direction of fluid flow for left-right determination

Takanobu A. Katoh^{1,2*}, Toshihiro Omori^{3*}, Katsutoshi Mizuno^{1†}, Xiaorei Sai¹, Katsura Minegishi^{1†}, Yayoi Ikawa¹, Hiromi Nishimura¹, Takeshi Itabashi⁴, Eriko Kajikawa¹, Sylvain Hiver¹, Atsuko H. Iwane⁴, Takuji Ishikawa³, Yasushi Okada^{5,6}, Takayuki Nishizaka², Hiroshi Hamada^{1*}

Zebrafish



Katoh *et al.*, *Science* **379**, 66–71 (2023)

Limitations of the two prevailing models

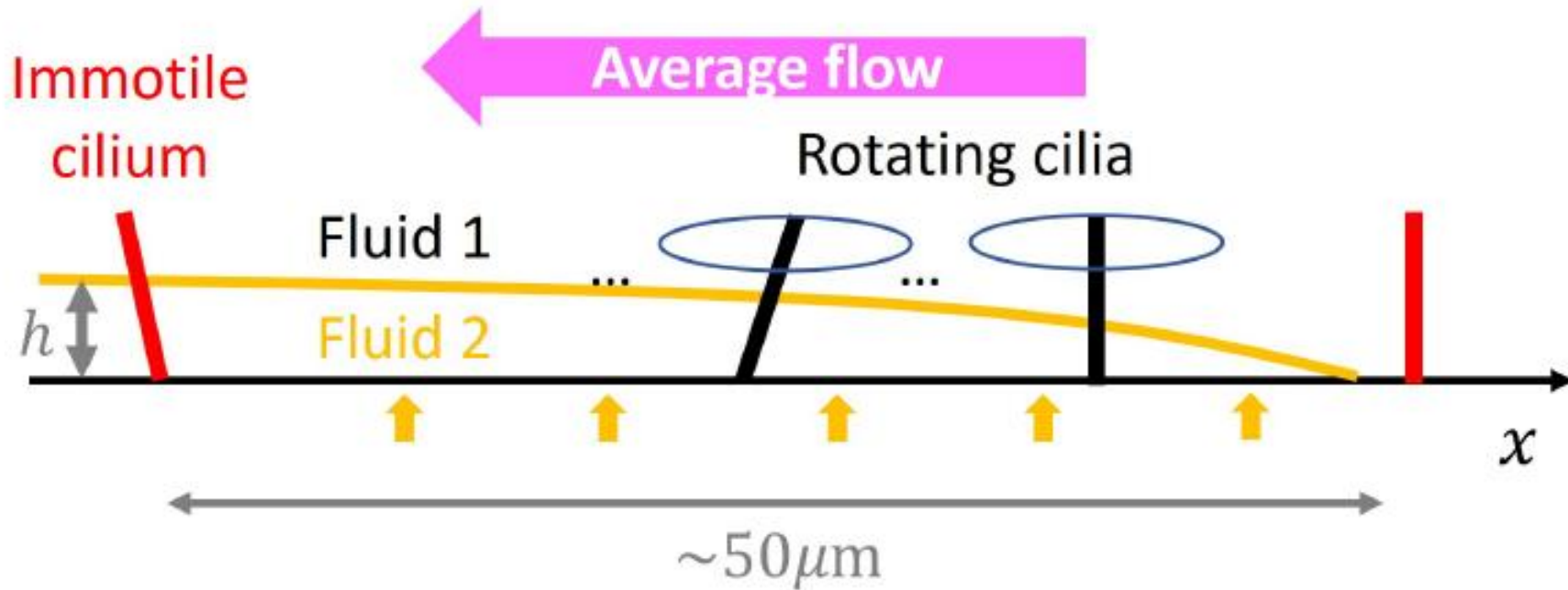
Chemosensing model

- ignores sufficiency of sensory cilia
- signal identity unresolved

Mechanosensing model

- near-symmetric signal problem
- short-range r^{-3} decay → unclear role of central cilia

A unifying physical mechanism

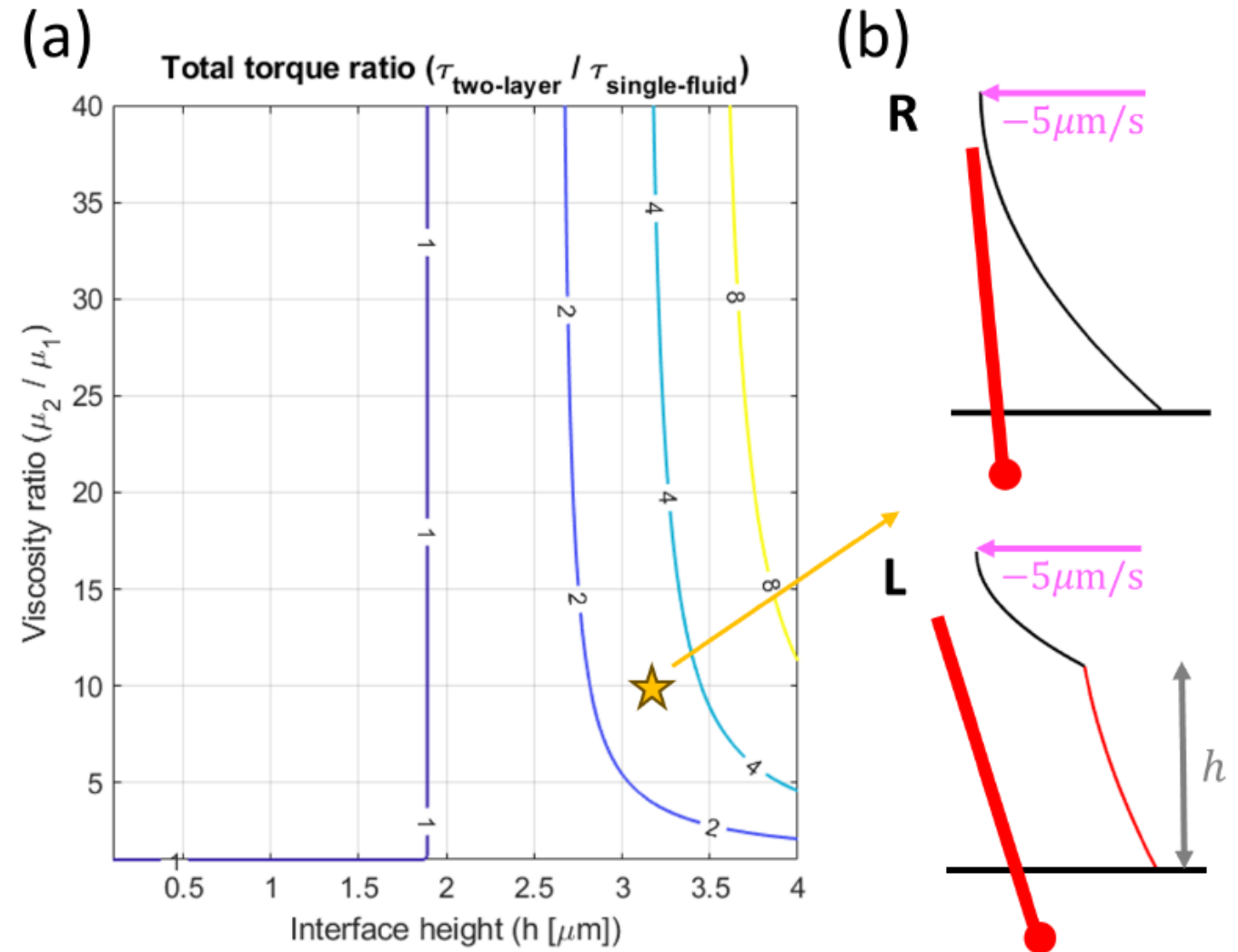


C.F. Lee and J. Vermot (2025)

Viscosity-mediated signal amplification enables robust left-right symmetry breaking in the mouse node

[bioRxiv 2026.01.13.699291](https://doi.org/10.1101/2026.01.13.699291)

Robust amplification of the left-right differentiating signal



C.F. Lee and J. Vermot (2025)

Viscosity-mediated signal amplification enables robust left-right symmetry breaking in the mouse node

[bioRxiv 2026.01.13.699291](https://doi.org/10.1101/2026.01.13.699291)

How the unified mechanism resolves both models

- **Symmetric flow is no longer a problem:** near-symmetric flow magnitudes can still produce amplified mechanical asymmetry
- **Central motile cilia gain a clear role:** they both sustain flow and build the viscous near-surface layer
- **Immotile cilia become the decisive sensors:** they detect the amplified torque/stress that breaks symmetry
- **Chemical identity no longer matters:** secreted macromolecules act mechanically by increasing near-surface viscosity

Summary of Story 1

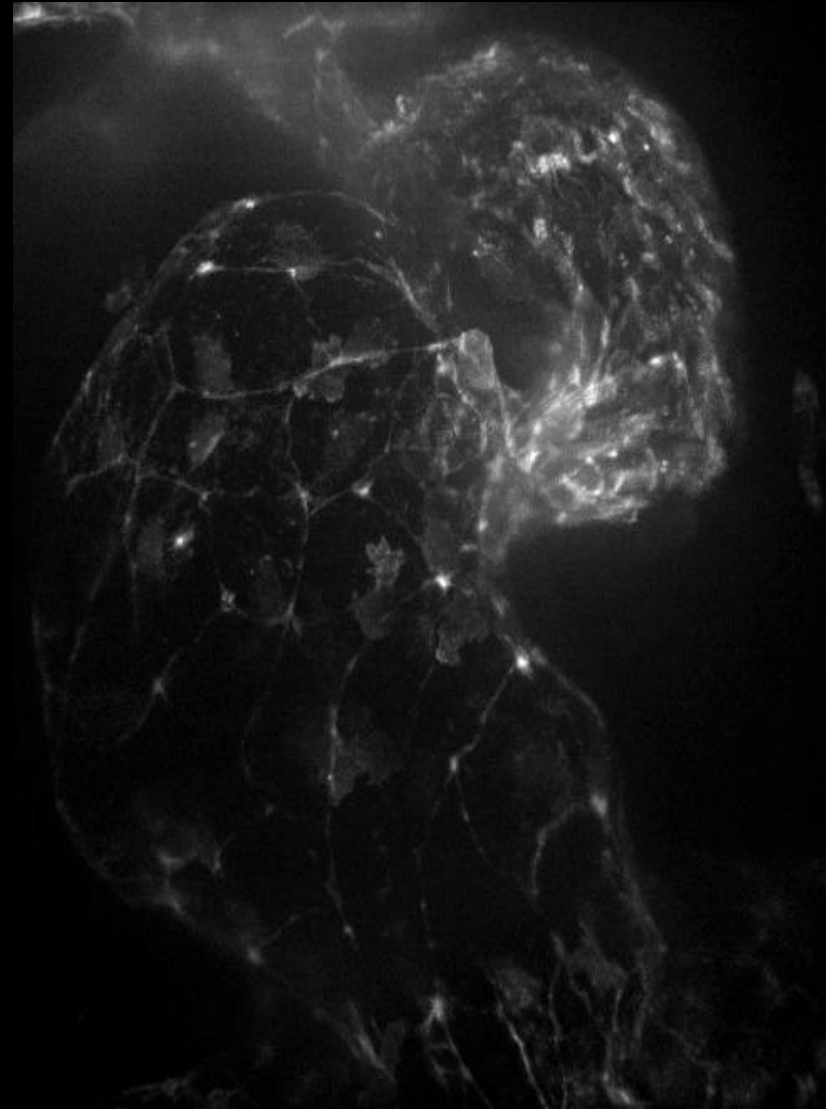
Molecular chirality at the tissue scale

→ directional flow + collective secretion

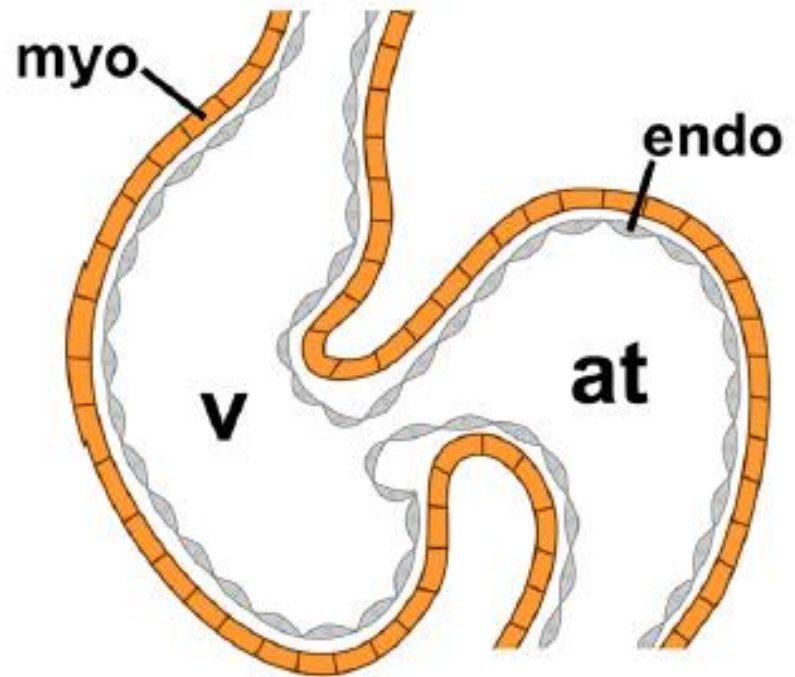
→ robust left-right symmetry breaking

Once symmetry is broken, the heart begins to form. But another puzzle emerges at the tissue scale → onto our second story

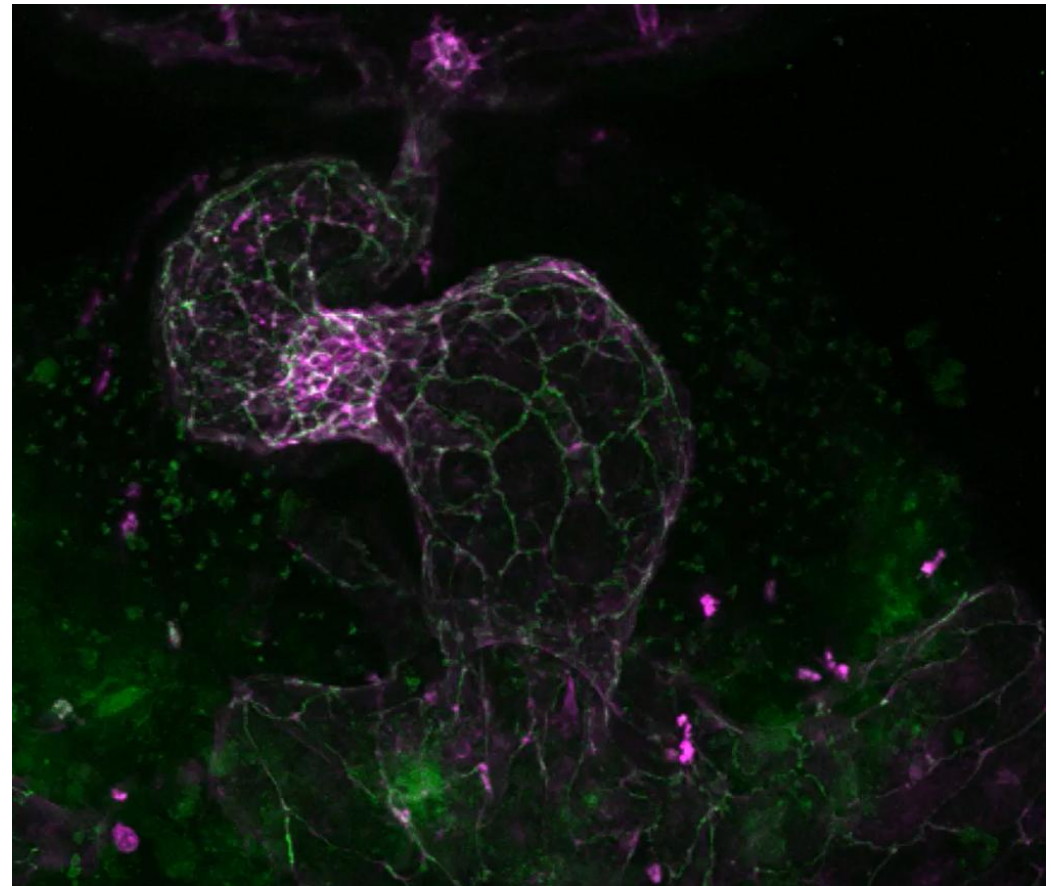
Story 2: Endocardium cell shapes



Vermot lab (Imperial College)



González-Rosa (2022)
Circulation Research

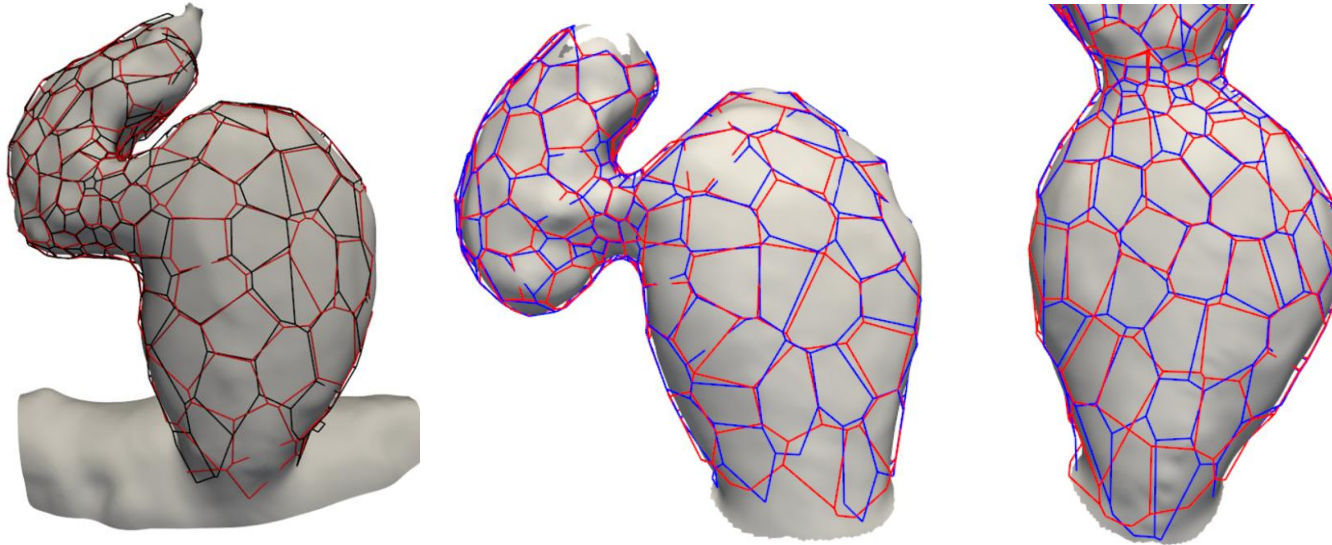


ZF endocardium 48 hours post fertilization (Vermot lab)
Pink: VE-cad; green: actomyosin

And we noticed that ...

Black/blue: cell boundary

Red: cVT



Antoine Sanchez

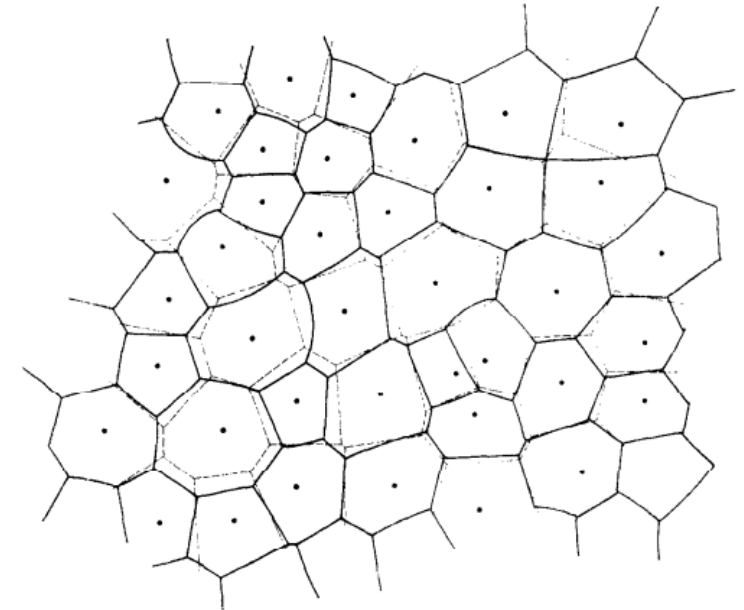
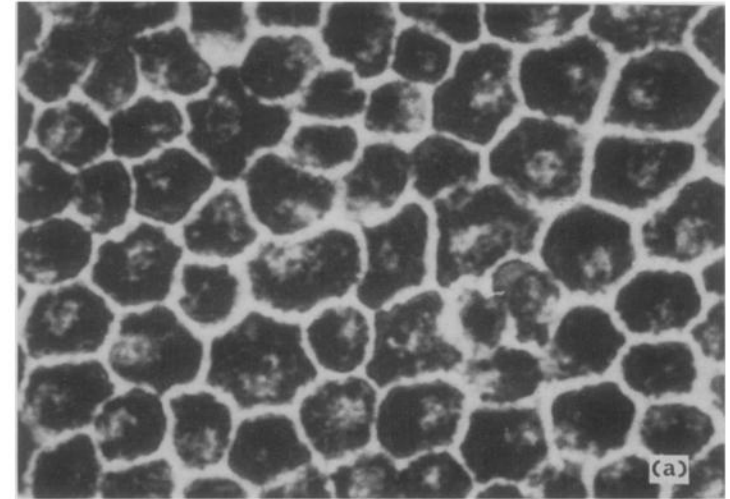


Sulaimaan Lim

ZF endocardium generally exhibits the so-called Centroidal Voronoi Tessellation (CVT)-like pattern

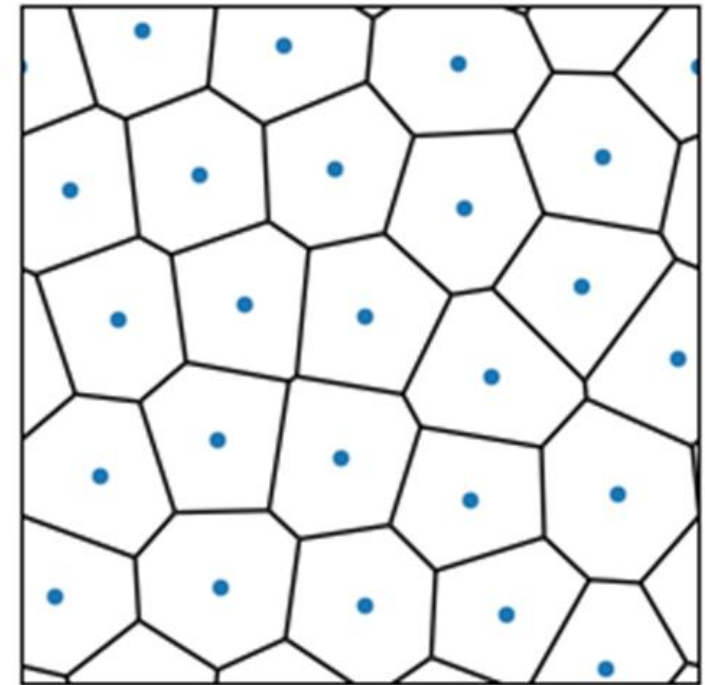
Voronoi Tessellations

- **Voronoi tessellation (VT):** Each region contains all locations closest to one “seed point” than to any other seed point
- In the 70s, Honda noticed that many epithelia cells resembled VTs



Centroidal VT

- **Centroidal Voronoi tessellation:** VT such that the seeds are also the centres of mass of the corresponding Voronoi cell
- **CVT is highly specific and is highly unlikely to be generated randomly**



Centroidal Voronoi tessellation (CVT)

Aside: Lloyd's algorithm, CVT, and quantizer energy

- **Quantizer energy:** $E_q = \sum_i \int_{V_i} |\mathbf{x} - \mathbf{c}_i|^2 dA$

measures the average squared distance from points in each cell to its seed

- **CVT = stationary points of the quantizer energy**
- **Lloyd's algorithm**
 1. Construct Voronoi tessellation from current seeds
 2. Move each seed to the centroid of its Voronoi cell
 3. Repeat
- **Global ground state (2D isotropic):** triangular seed lattice \leftrightarrow regular hexagonal Voronoi tiling [Gershgorin theorem in 2D]
- **But the energy landscape is nonconvex:** many metastable local minima

Puzzle: Why do endocardial cell shapes organize into a CVT pattern?

Approach: Vertex model

Vertex model (VM) is the standard cell-level modelling tools for polygonal cells

And is based on the energy:

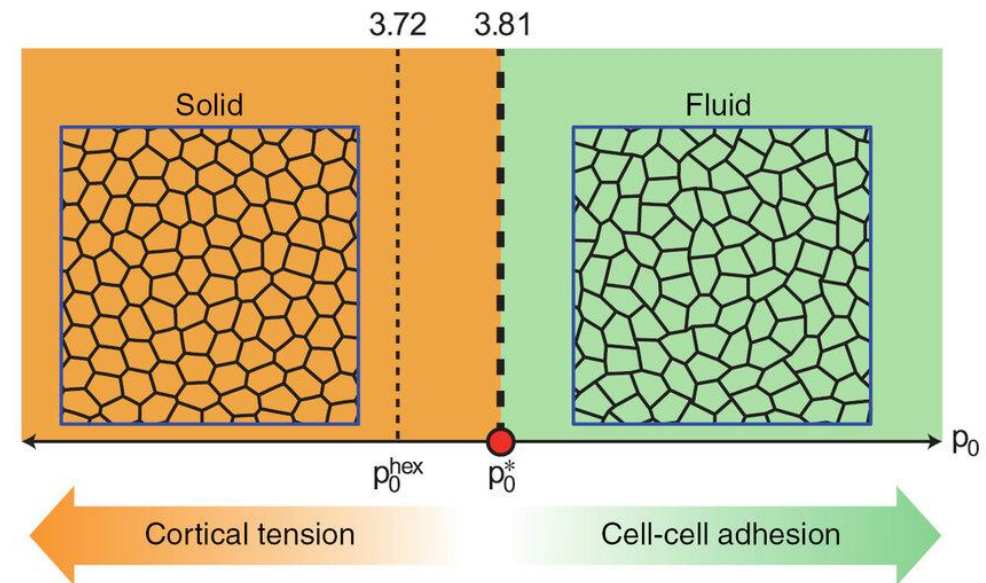
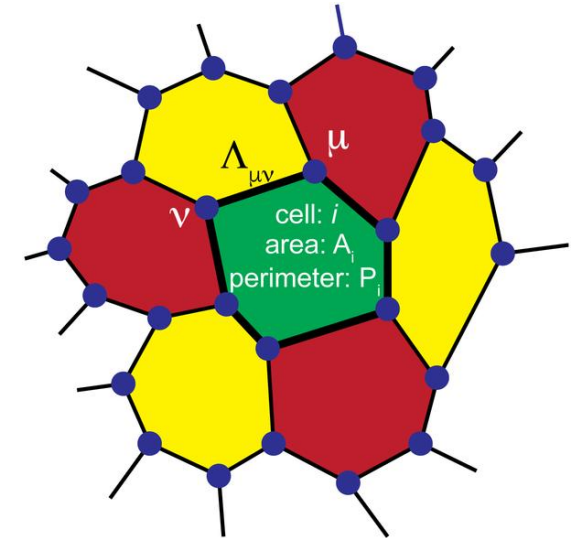
$$E = \sum_{i=1}^N \left[\frac{1}{2} K_A (A_i - A_0)^2 + \frac{1}{2} K_P (P_i - P_0)^2 \right]$$

A preferred area

A preferred perimeter: trade-off between adhesion proteins & cortical tension

Shape index: $p_0 = \frac{P_0}{\sqrt{A_0}}$

Fig from Barton et al (2017) PLoS Comp Biol



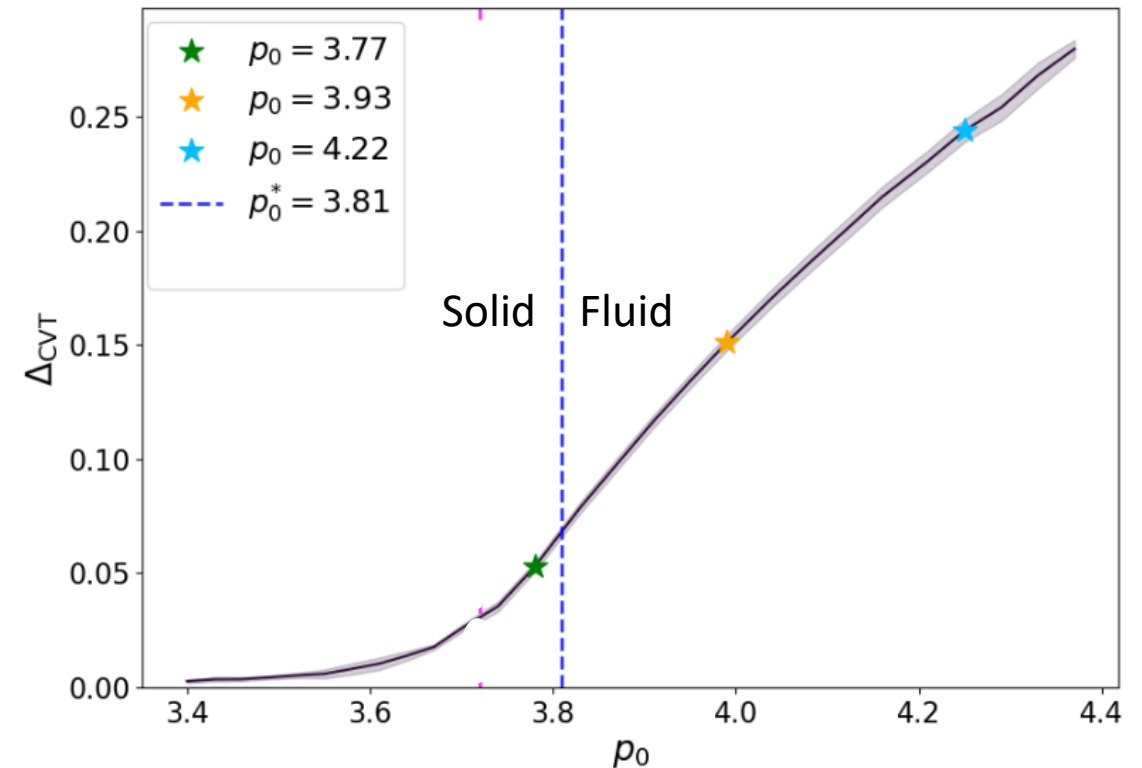
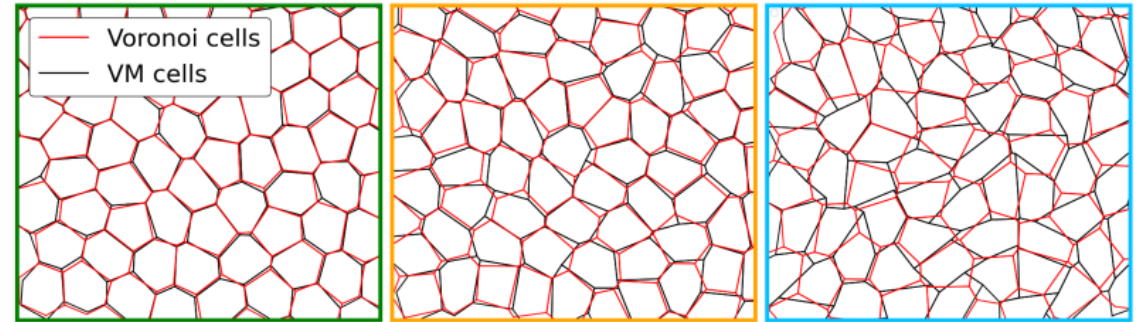
Bi, Lopez, Schwarz & Manning et al (2015) Nat Phys

Shape index vs CVT

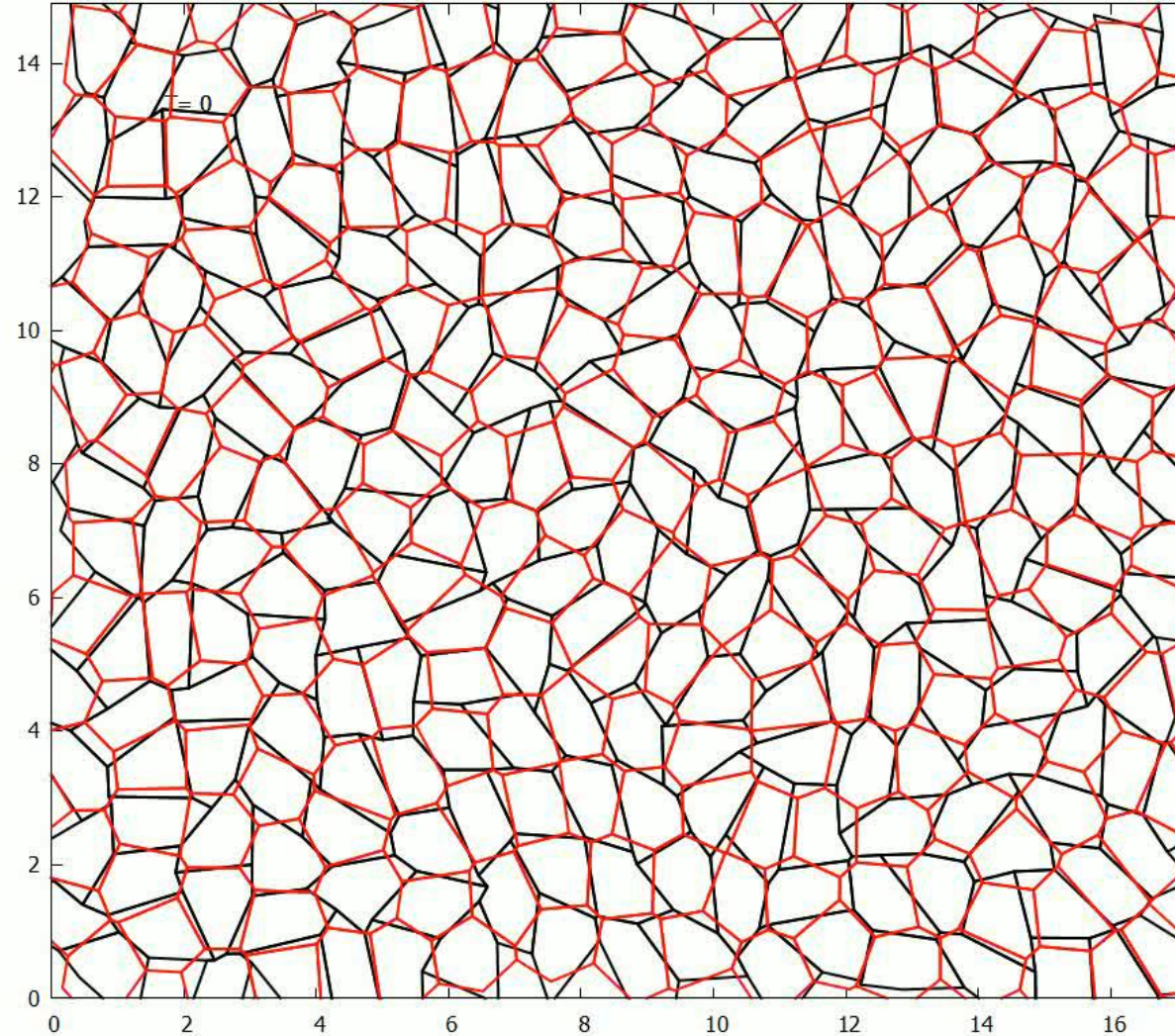
But many endocardial cells do not have low shape index – unlike tissues in the solid phase

→ standard vertex model doesn't seem to work

We therefore asked: “what does a heart do?”

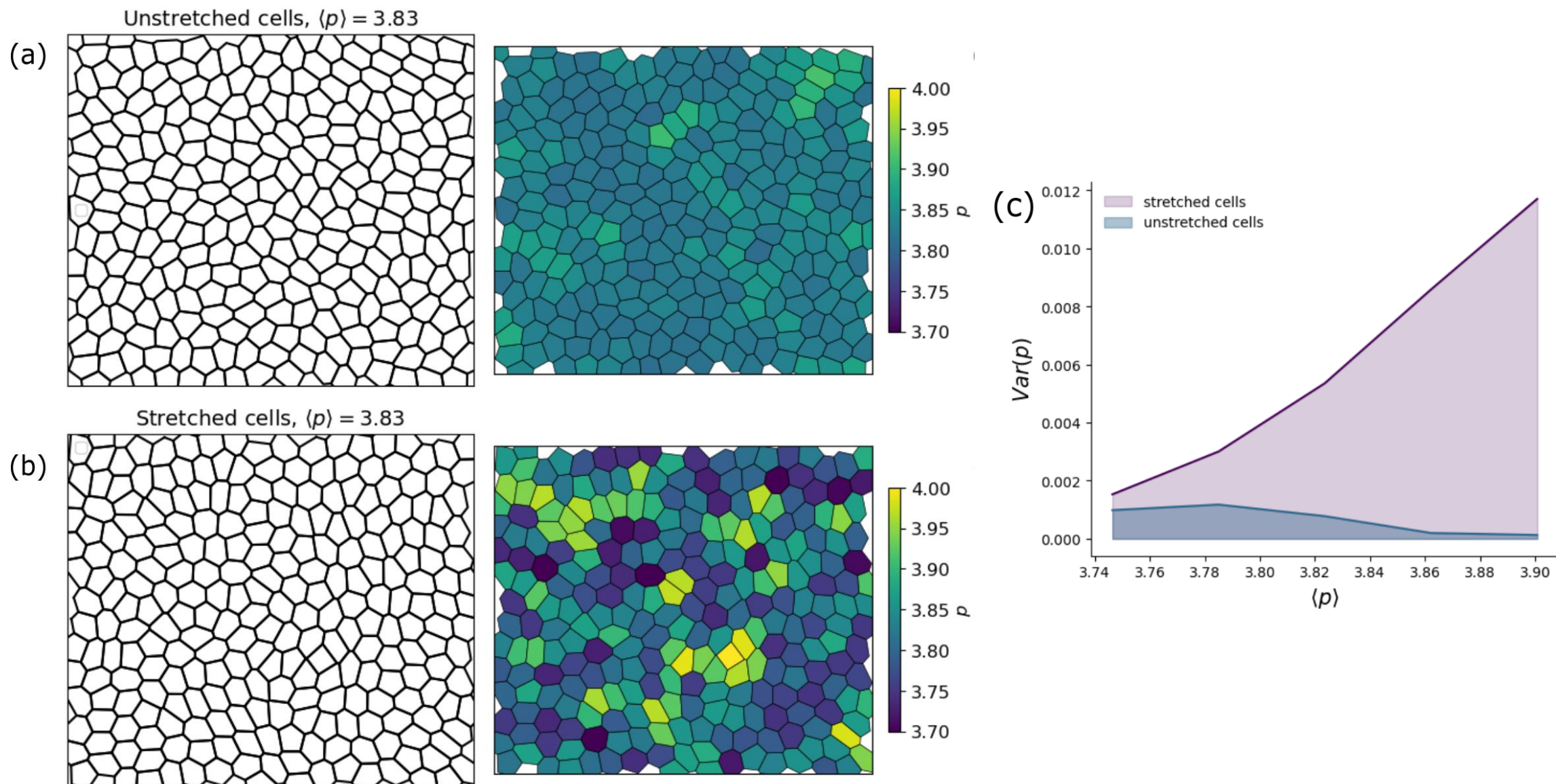


High-frequency periodic stretching leads to CVT



Black: cell boundary
Red: cVT

High-frequency periodic stretching preserves diverse cell shapes



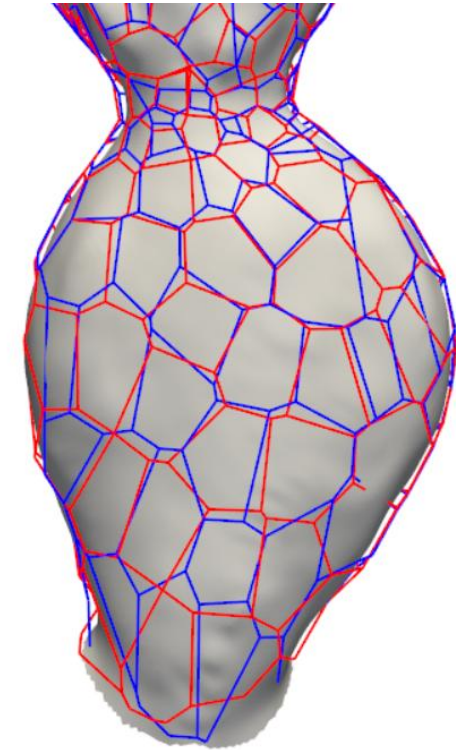
Proposed mechanism

- **Baseline:** generic endothelium starts with relatively high mean shape index
- **Heartbeat forcing:** periodic stretch mechanically anneals the tissue toward CVT-compatible packing
- **High frequency:** incomplete relaxation preserves cell shape variability
- **Outcome:** global CVT-like order with diverse individual cell shapes

Summary of Story 2

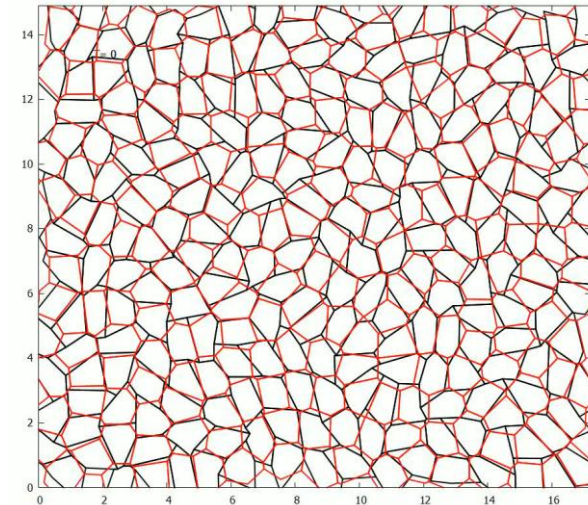
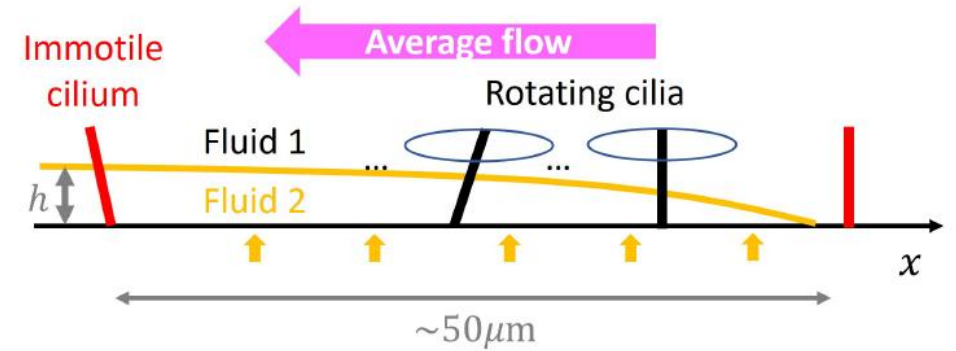
Puzzle: Why do endocardial cell shapes organize into a CVT pattern?

'Solution': High-frequency periodic stretching enables simultaneous CVT-like pattern and diverse cell shapes



Conclusion

- Story 1: viscous amplification enables robust left-right determination
- Story 2: periodic forcing leads to CVT-like pattern with diverse cell shapes



Common thread: How minimal nonequilibrium physical mechanisms robustly pattern the developing heart across scales

Outlook

Q1: Not all LR determinations are cilia-based, what are other key mechanisms that transmit molecular chirality to macroscopic chirality?

Q2: Why does the vertex model work at all? Do cell areas and perimeters happen to be the right minimal variables for determining tissue behaviour?

- A PhD position is available to start in Autumn 2026, open to all nationalities
Details on clee.bg-research.cc.ic.ac.uk/index.html, also on findaphd.com

Thank you for your attention