Wrinkling of epithelial shells: experiments, models, simulations

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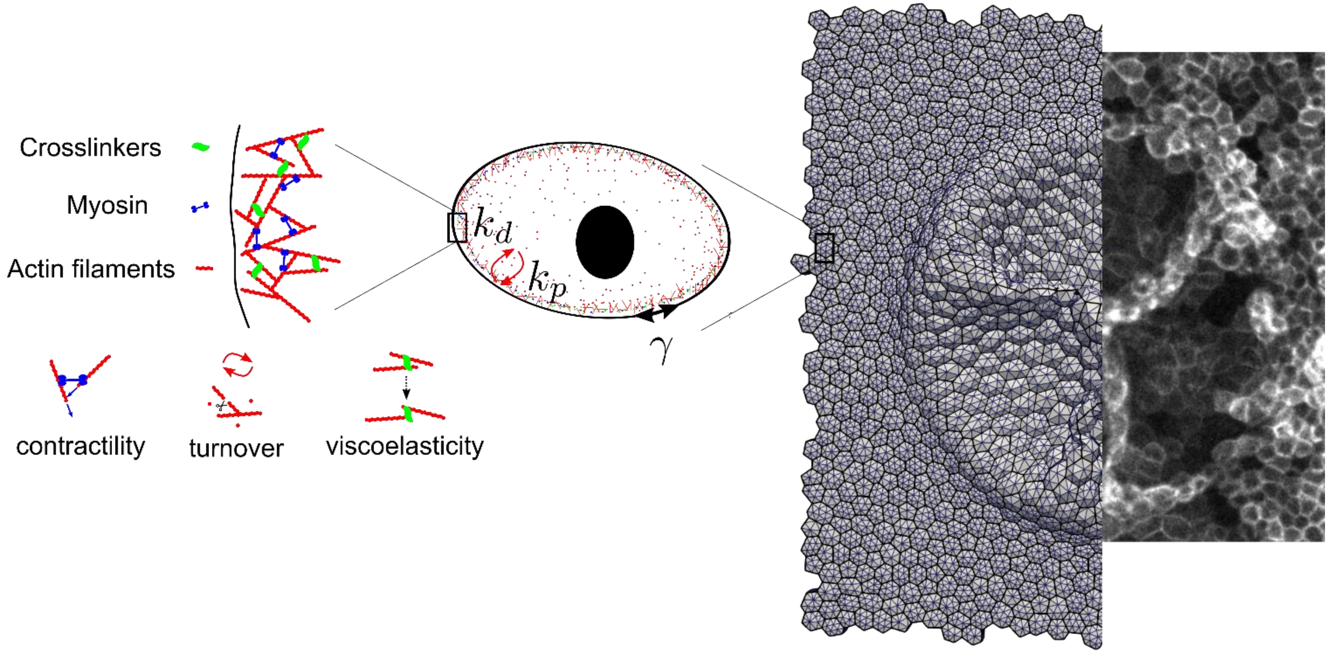

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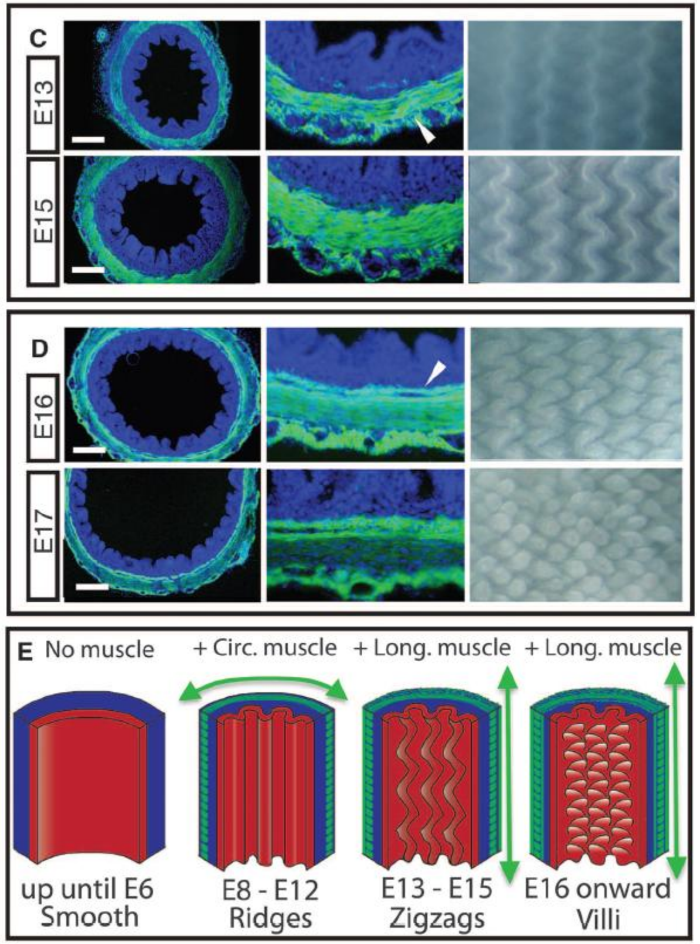
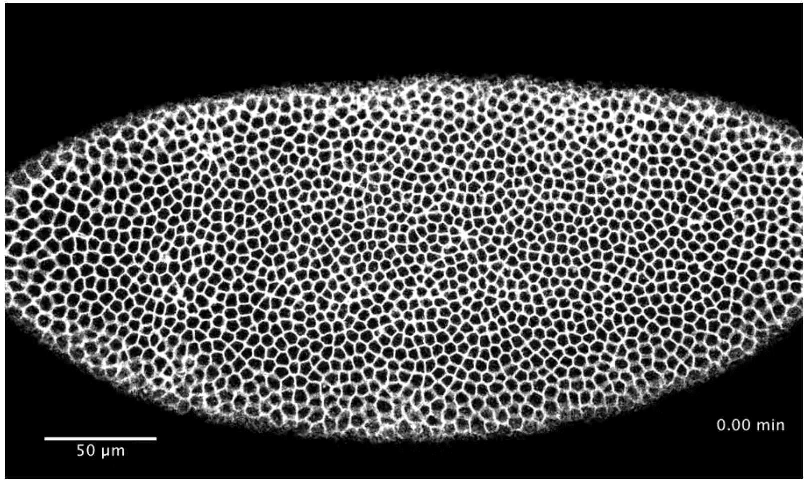
Outline

- Biological context
- *In vitro* experiments
- Vertex model
- Continuum approximation

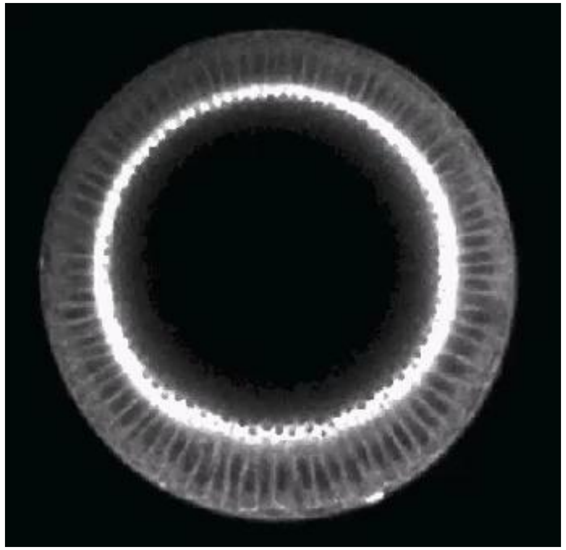
Mechanical instabilities as a driver of epithelial morphogenesis



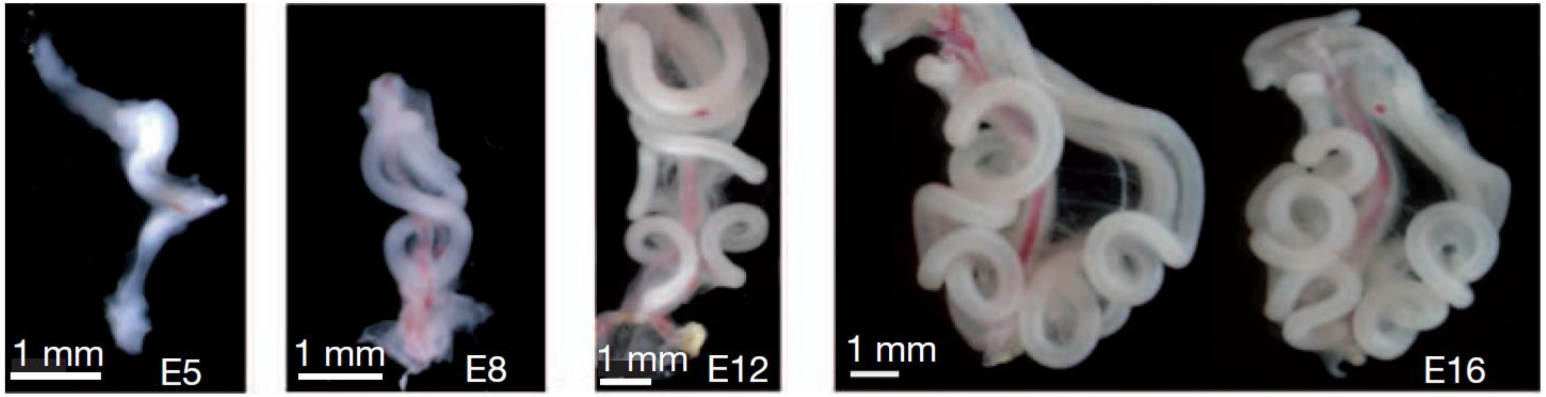
Shyer et al., Nature, 2011



Kazsa lab



Brodland et al., PNAS, 2010



Savin et al., Nature, 2011

-> fit as much surface area as possible in a confined space

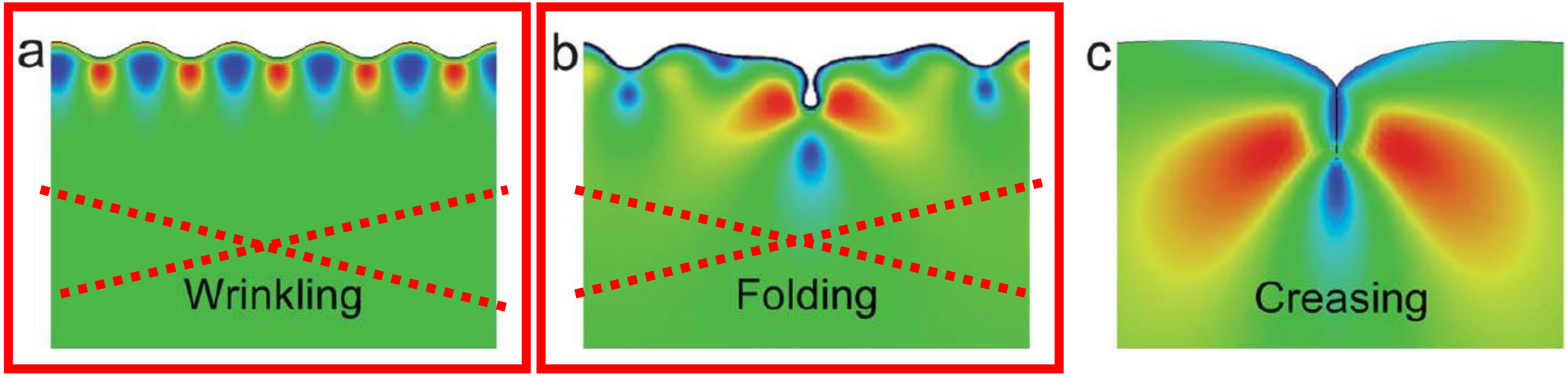
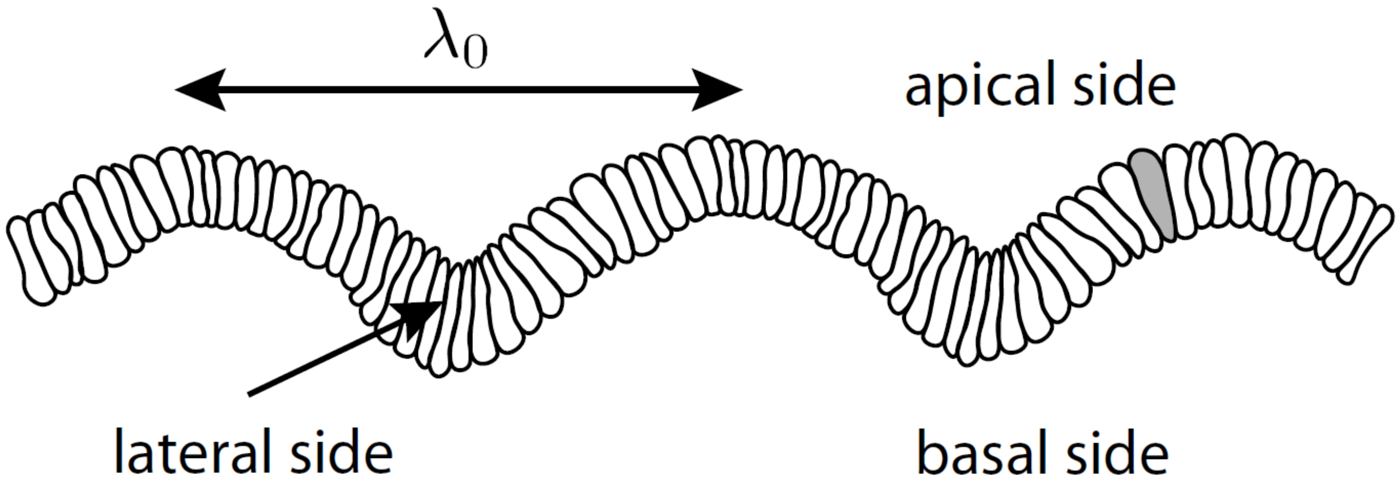


Fig. 1 Schematic of three types of morphological instability: (a) wrinkling, (b) folding, and (c) creasing.

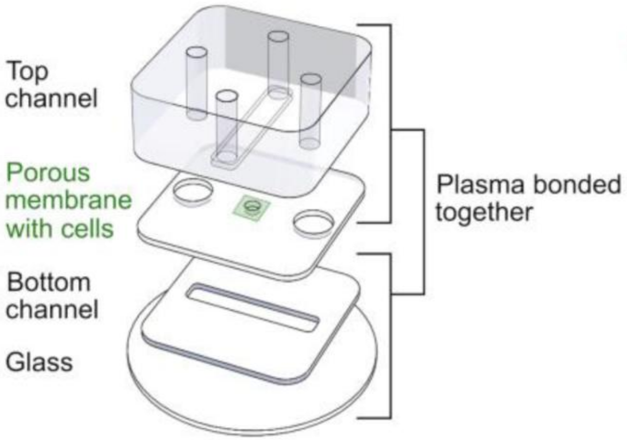
Li et al., Soft Matter, 2012

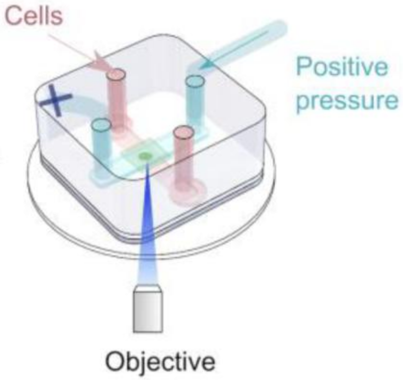


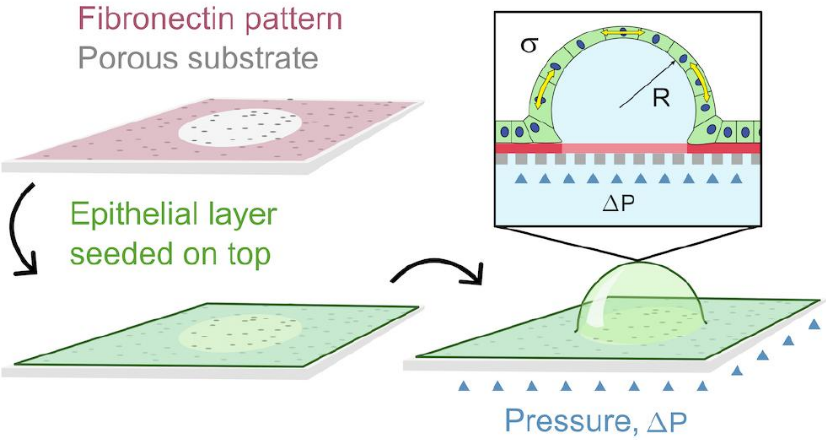
Wrinkling of unsupported monolayer in viscous medium

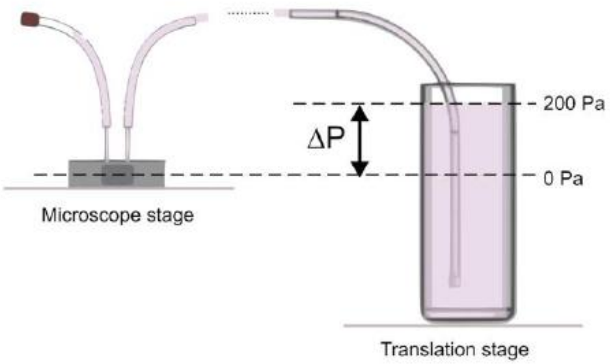
Andrensek et al., PRL, 2023

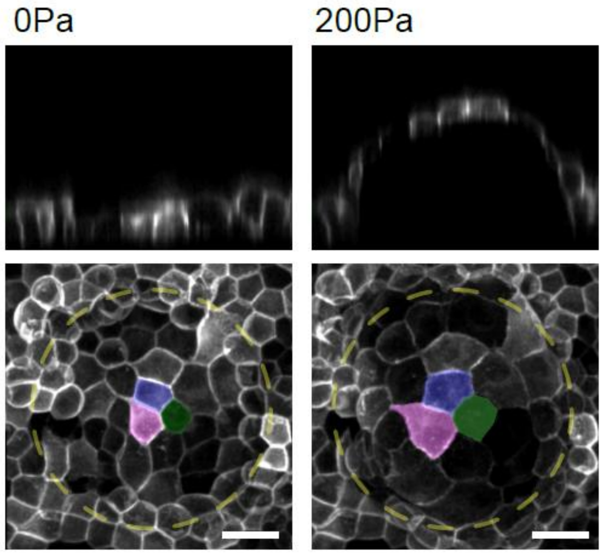
Dynamical control of suspended monolayers

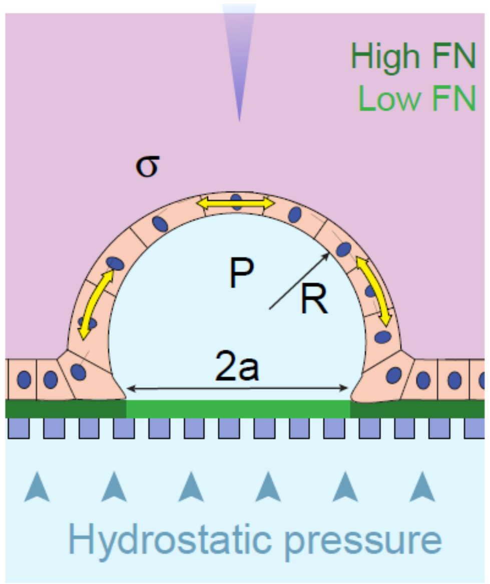


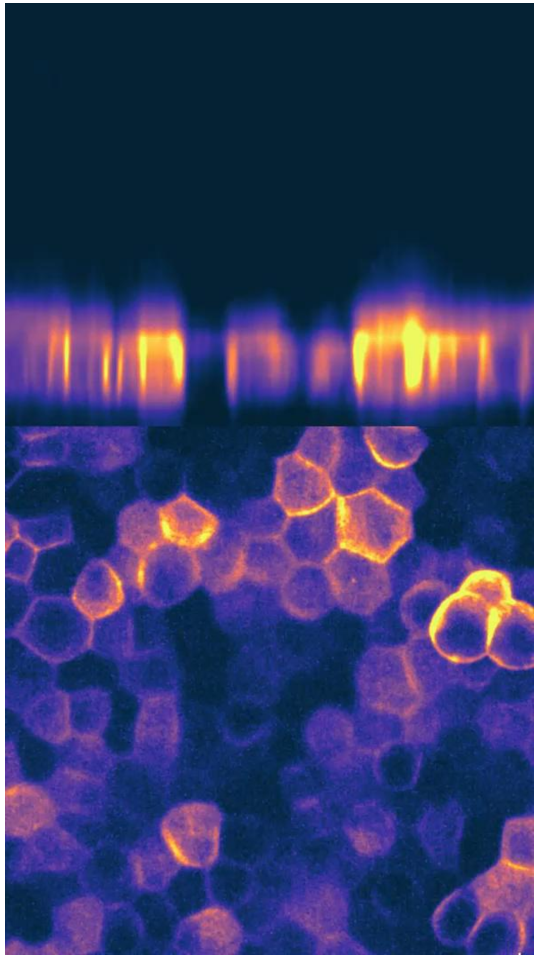








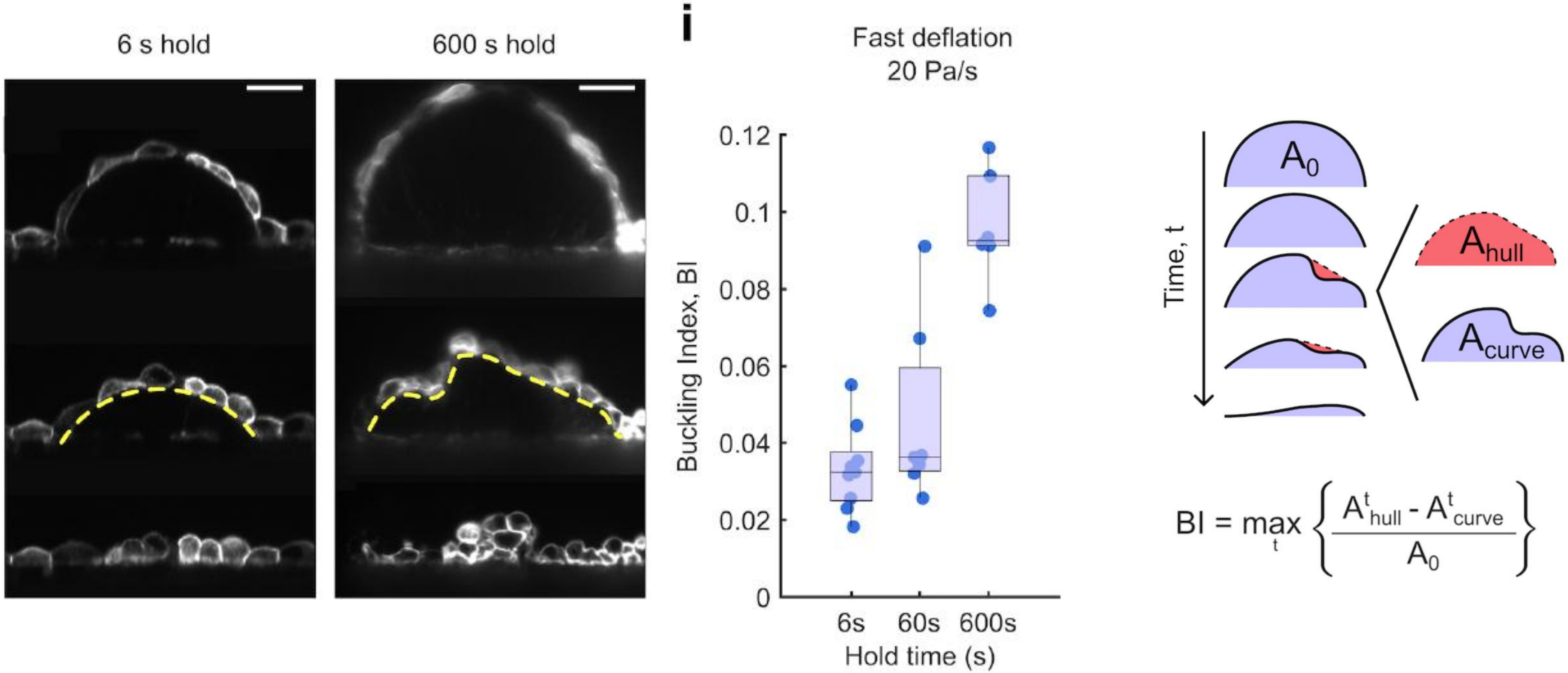




MOLI : Monolayer Inflator

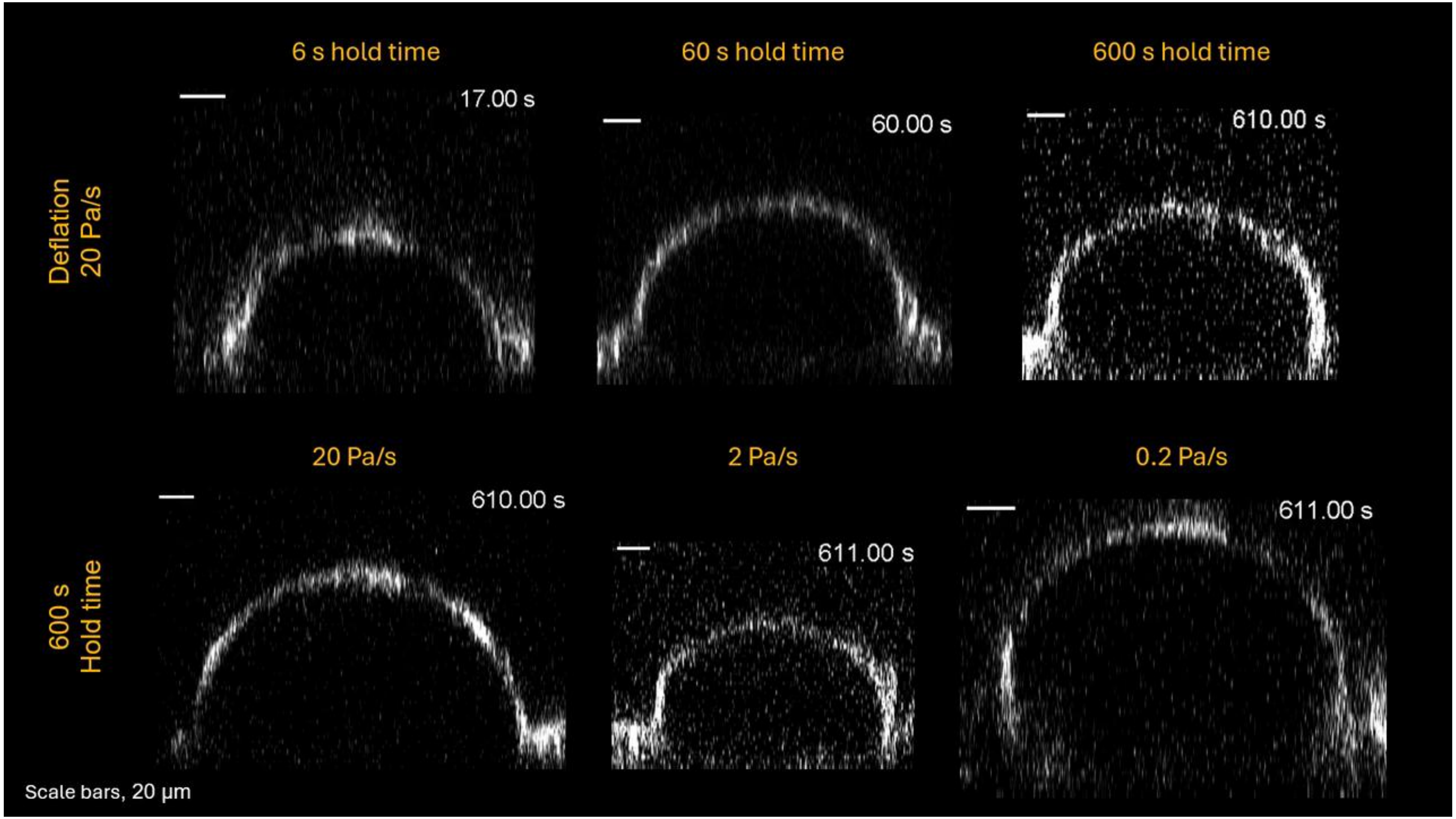
Chahare et al., bioRxiv., 2025

Buckling depends on hold time



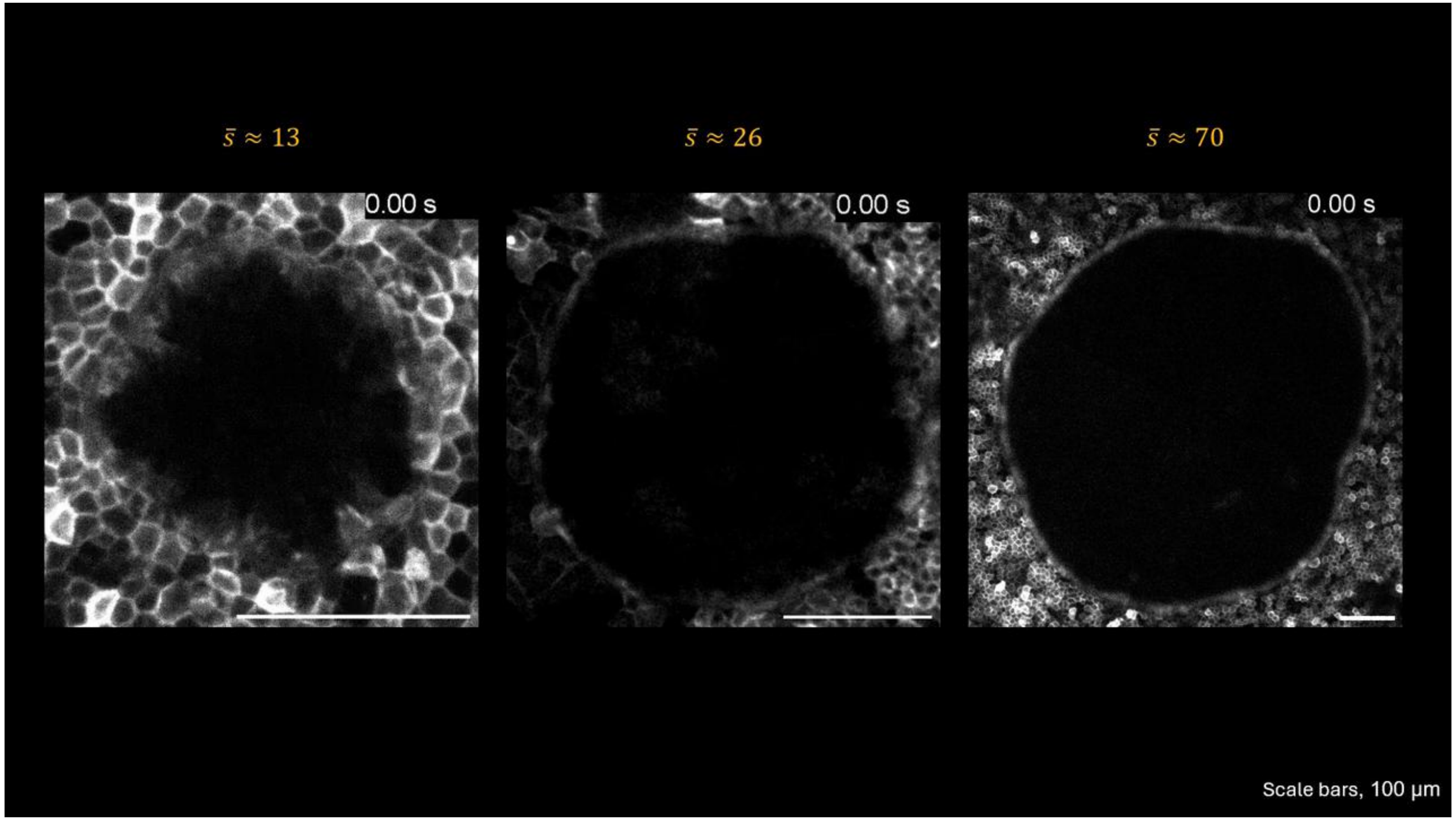
Chahare et al., bioRxiv., 2025

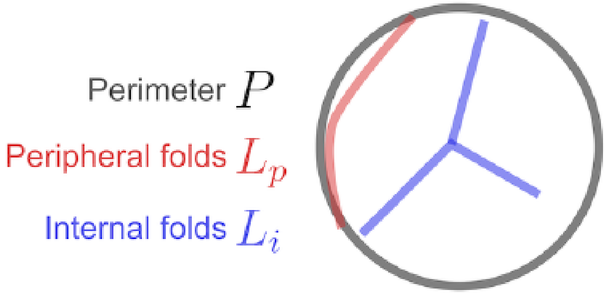
Buckling depends on deflation rate and hold time



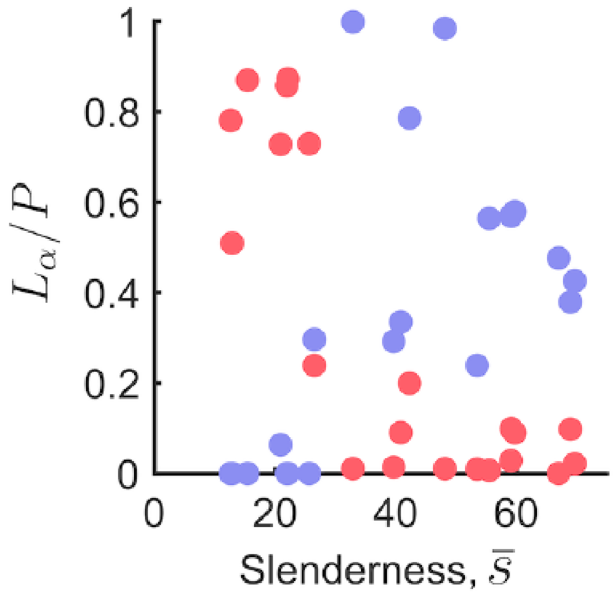
Chahare et al., bioRxiv., 2025

Symmetry-breaking and wrinkling pattern

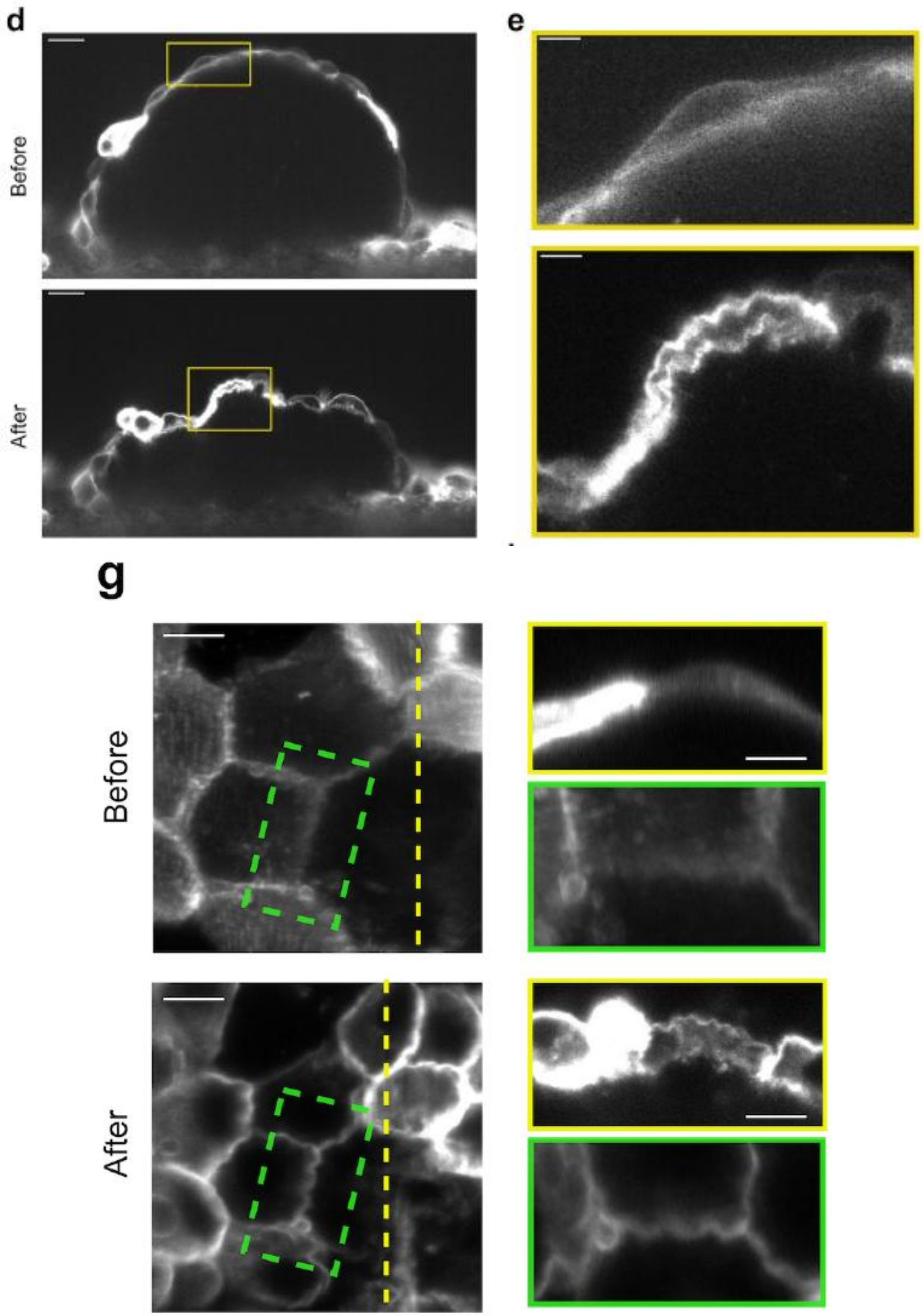




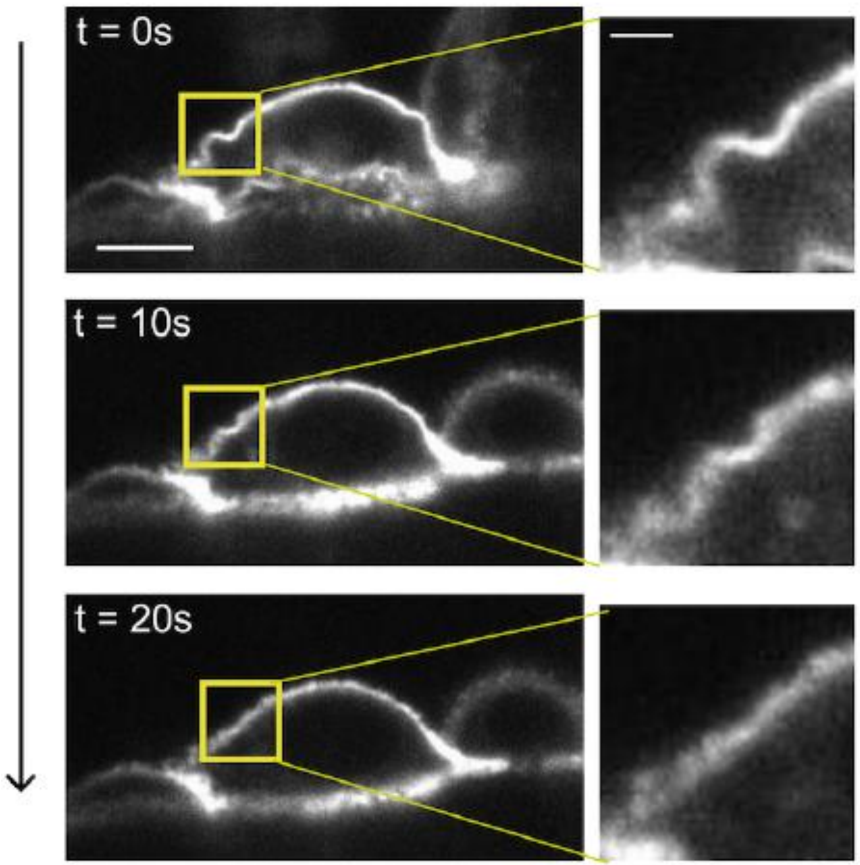
L_α / P , where $\alpha = p, i$

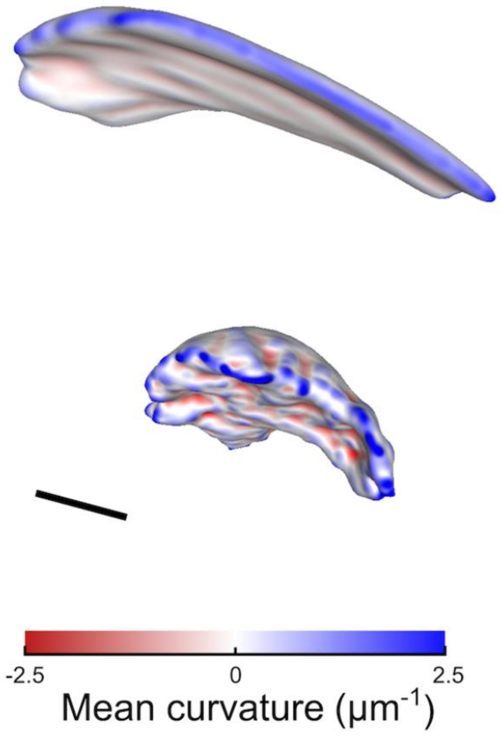


Chahare et al., bioRxiv., 2025



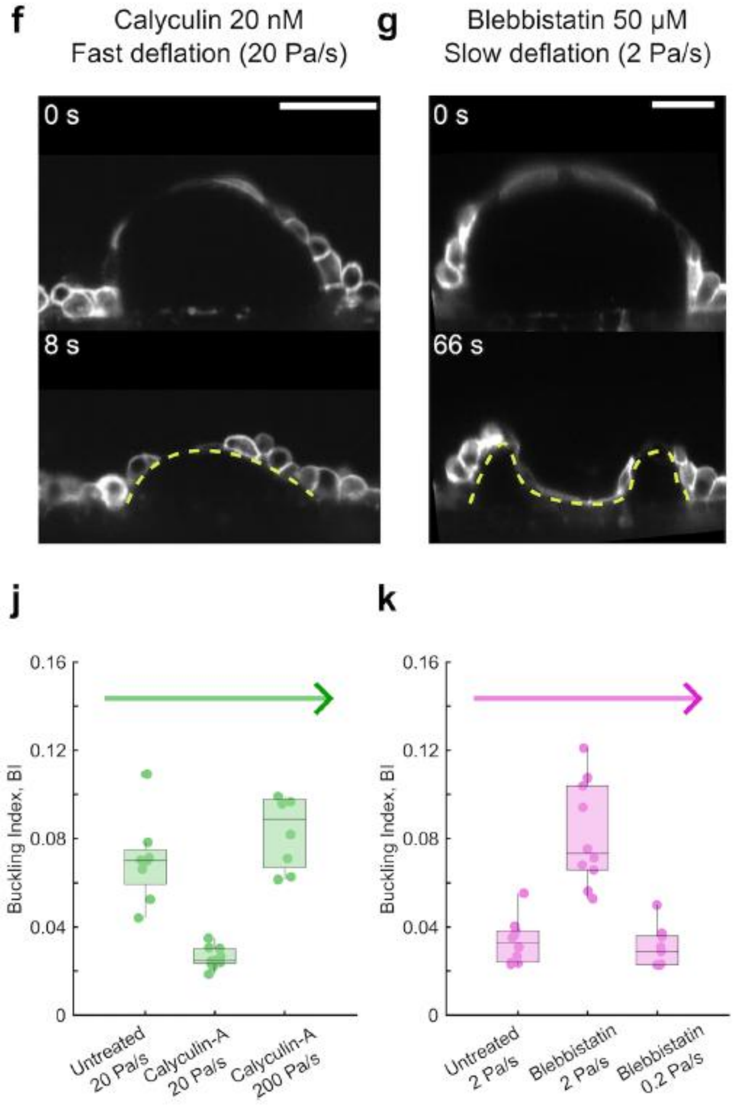
Wrinkling at multiple scales

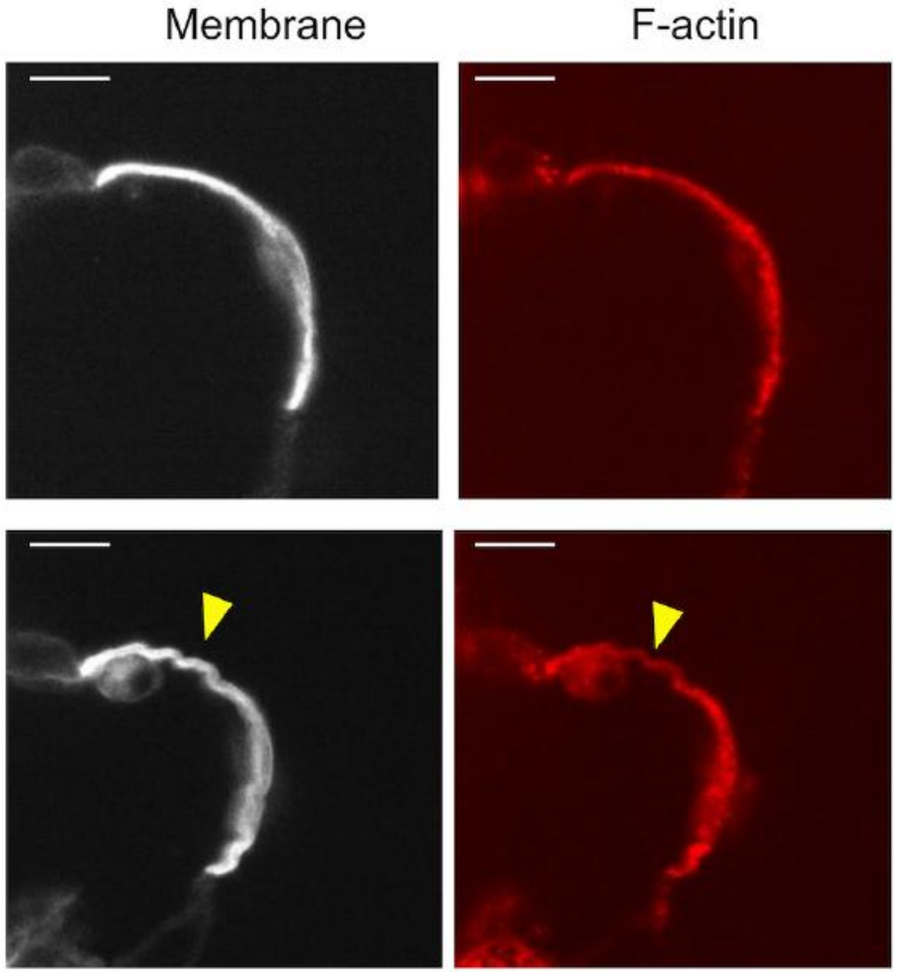




Chahare et al., bioRxiv., 2025

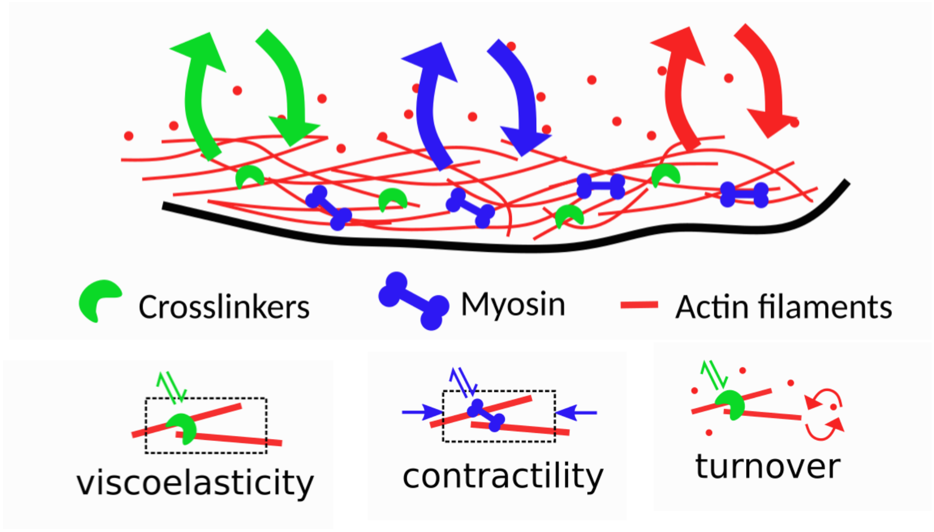
Buckling depends on the actomyosin cortex dynamics



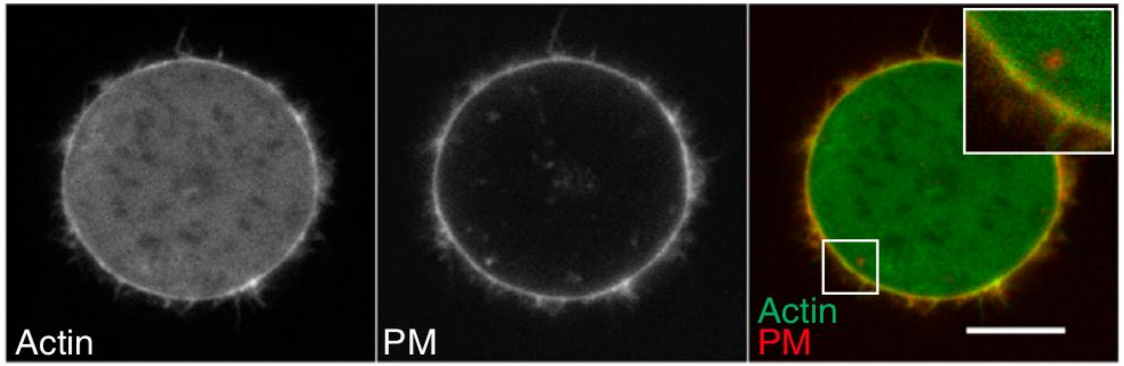


Chahare et al., bioRxiv., 2025

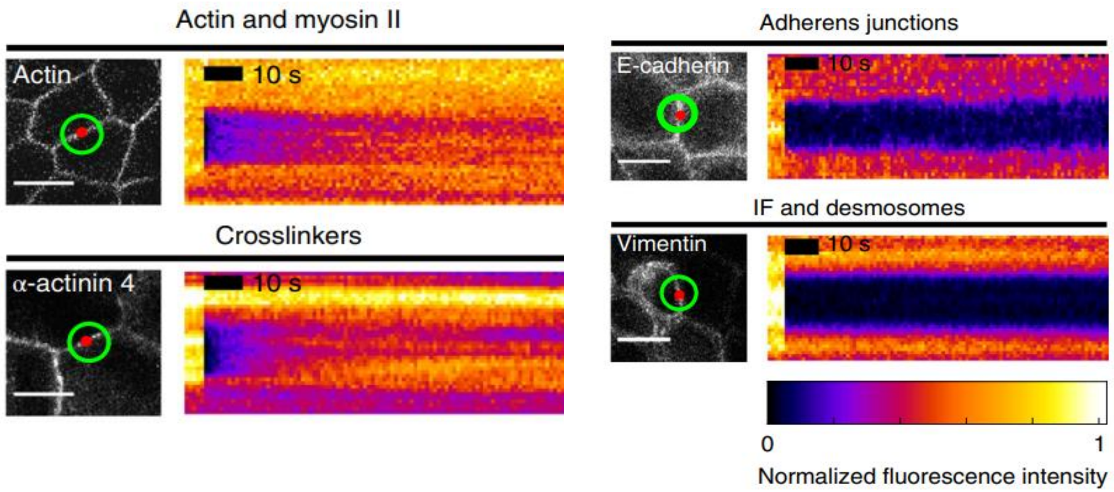
Actomyosin cortex



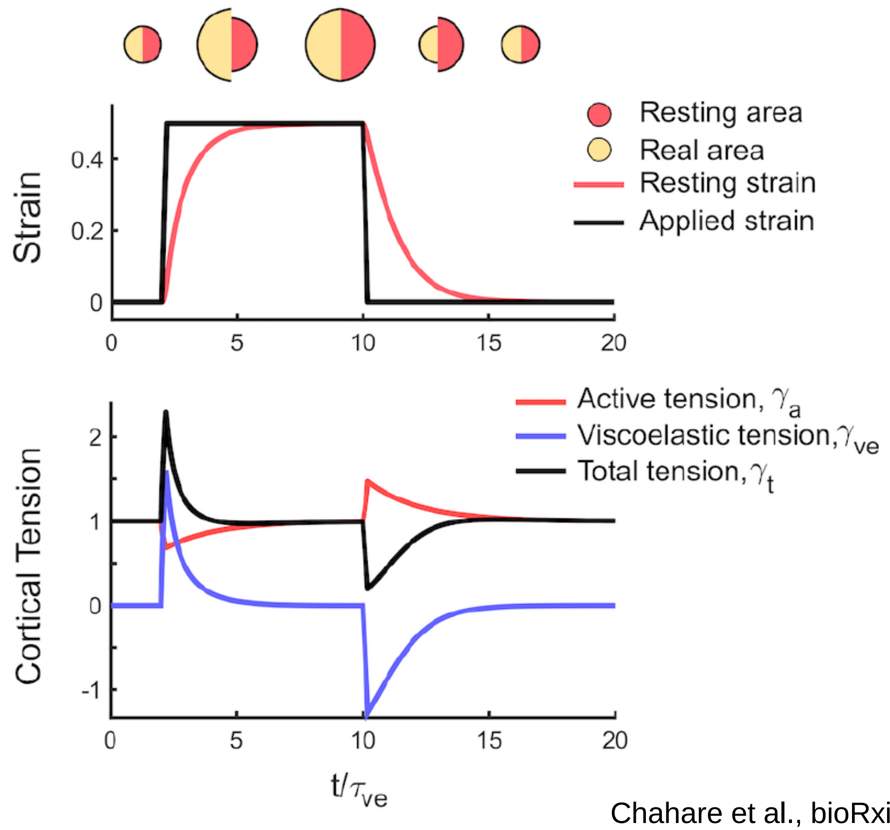
Ouzeri et al., bioRxiv., 2025



Clark, Dierkes, Paluch, Biophys. J., 2013

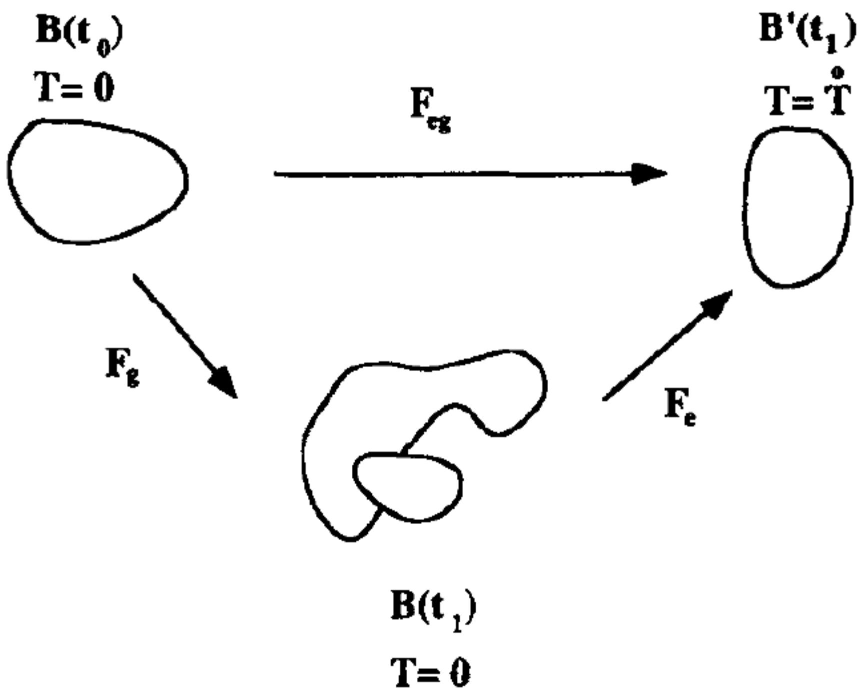


Khalilgharibi et al. Nat. Phys., 2019

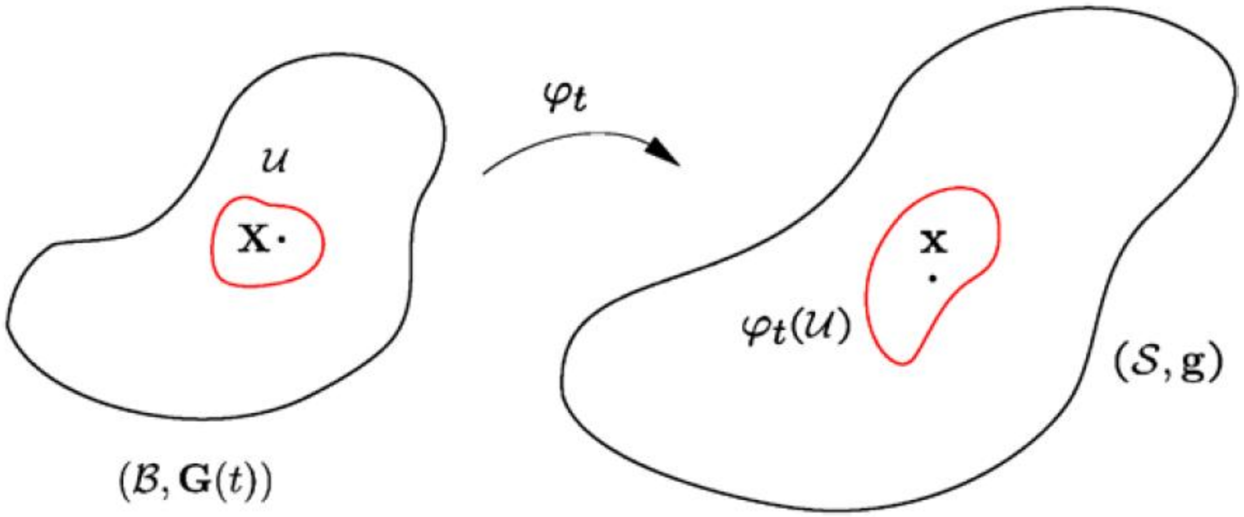


Chahare et al., bioRxiv., 2025

Geometric approach to elastic growth (morphoelasticity)



Rodriguez et al., J. Biomechanics, 1994



-> Riemannian manifold whose metric is related to the growth and with respect to which strains should be measured

-> Time-dependent stress-free configuration

-> Evolution law ?

Yavari, J. Nonllinear Sci., 2010

Onsager's variational principle

- Coupling multiple physics at multiple scales
- Applicable to a wide variety of biological settings
- Thermodynamically consistent models by construction

State and process variables

$$X, V \qquad \partial_t X = V \text{ or } \partial_t X = P(X)V$$

Rate of change of free energy

$$\frac{dF(X(t))}{dt} = D_X\mathcal{F}(X)P(X)V$$

Dissipation potential $\mathcal{D}(X;V)$

Power input $\mathcal{P}(X;V) = -F(X)V$

$$\mathcal{L}(X;V,\Lambda) = \mathcal{R}(X;V) + \Lambda \cdot \mathbb{C}(X)V$$

$$\{V,\Lambda\} = \underset{W}{\operatorname{argmax}}\,\underset{\omega}{\operatorname{argmin}}\,\left[\mathcal{L}(X;W,\omega)\right]$$

1rst and 2nd order (necessary) optimality conditions $\boxed{\partial_V\mathcal{R} = 0 \qquad \partial_V^2\mathcal{R} = \partial_V^2\mathcal{D} \geq 0}$

governing equations 2nd law of thermodynamics

Mirza et al., New J. Phys., 2025

Gradient flows

Definition

A gradient system is a triple $(\mathcal{Z}, \mathcal{F}, \mathcal{D})$ where $\mathcal{Z}$ is a manifold with a differentiable structure, $\mathcal{F} : \mathcal{Z} \to \mathbb{R}$ a functional driving the dynamics of the system and $\mathcal{D}(z, \cdot) : T_z\mathcal{Z} \to \mathbb{R}$ a non-negative convex dissipation potential such that $\mathcal{D}(z, 0) = 0$.

Definition

A solution is a curve $\mathrm{z} : \mathrm{I} \subset \mathbb{R} \to \mathcal{Z}$ solving the following gradient flow equation

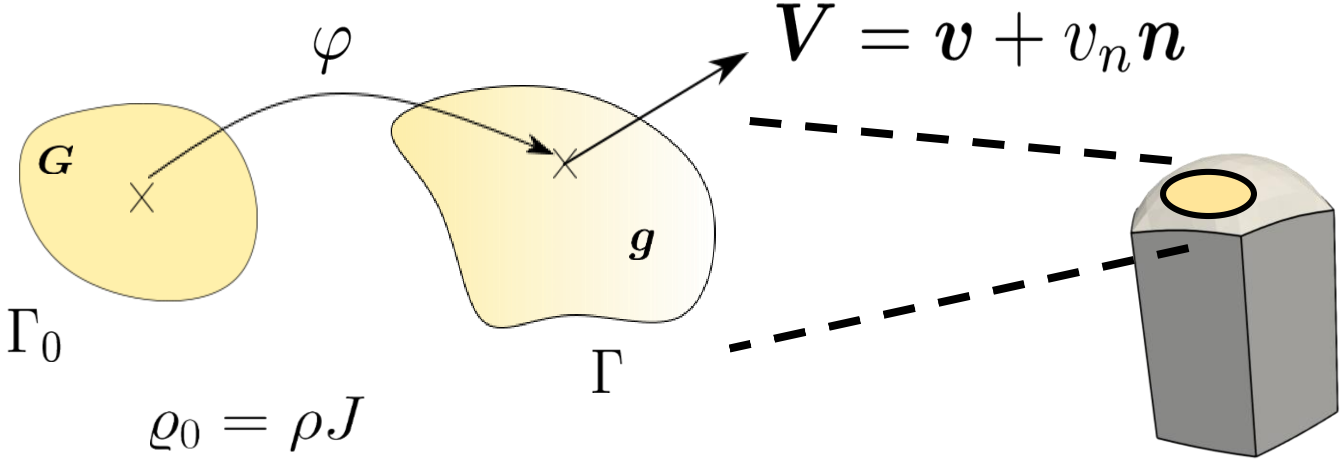
$$\mathcal{G}(\mathrm{z})\dot{\mathrm{z}} = -\mathrm{D}\mathcal{F}(\mathrm{z}) \text{ in } \mathrm{T}^*_\mathrm{z}\mathcal{Z}$$

- $\mathcal{Z} \to$ state space
- $\mathcal{F} \to$ (free) energy
- $\mathcal{D}(\mathrm{z}, \dot{\mathrm{z}}) = \frac{1}{2}\langle \mathcal{G}(\mathrm{z})\dot{\mathrm{z}}, \dot{\mathrm{z}} \rangle$ where $\mathcal{G}(\mathrm{z}) : \mathrm{T}_\mathrm{z}\mathcal{Z} \to \mathrm{T}^*_\mathrm{z}\mathcal{Z}$ is symmetric positive definite

$$\longrightarrow \quad \frac{\mathrm{d}}{\mathrm{dt}}\mathcal{F}(\mathrm{z}) = \langle \mathrm{D}\mathcal{F}(\mathrm{z}), \dot{\mathrm{z}} \rangle = -\langle \mathcal{G}(\mathrm{z})\dot{\mathrm{z}}, \dot{\mathrm{z}} \rangle = -2\mathcal{D}(\mathrm{z}, \dot{\mathrm{z}}) \leq 0$$

Peletier, 2014
Arroyo et al., 2018
Ouzeri, GSI, 2025

Active-viscoelastic-gel description of the cortex



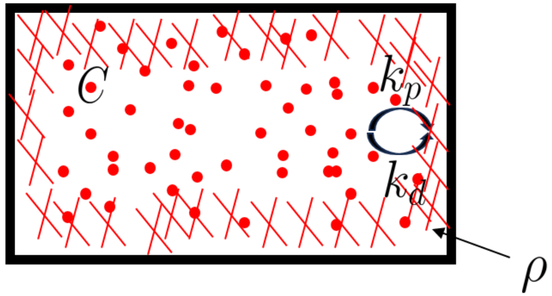
$$\boldsymbol{V} = \boldsymbol{v} + v_n \boldsymbol{n}$$

$$\varrho_0 = \rho J$$

$$\boldsymbol{C} = \varphi^*(\boldsymbol{g}) \quad \boldsymbol{d} = \frac{1}{2}(\nabla \boldsymbol{v} + \nabla \boldsymbol{v}^T) - v_n \boldsymbol{k}$$

$$\boldsymbol{E} = \frac{1}{2}(\boldsymbol{C} - \boldsymbol{G}) \longrightarrow \boxed{(\boldsymbol{C}, \boldsymbol{G})}$$

$$\frac{d\rho}{dt} + \rho(\nabla \cdot \mathbf{v} + \mathrm{v}_n H) = k_p C + k_d \rho$$ turnover



$$\mathcal{F} = \int_{\Gamma_0} \varrho_0 W(\boldsymbol{C}, \boldsymbol{G}) \, dS$$ elasticity

$$\mathcal{D} = \frac{\eta}{2} \int_{\Gamma_0} \varrho_0 \dot{\boldsymbol{G}} : \dot{\boldsymbol{G}} \, dS$$ remodelling

$$\mathcal{P} = \int_{\Gamma} \boldsymbol{\gamma} : \boldsymbol{d} \, dS$$ contractility

$$\boldsymbol{\gamma}(\rho) = \rho \xi \boldsymbol{I}$$

$$\mathcal{P}_e = -\int_{\partial \Gamma_N} \boldsymbol{t} \cdot \boldsymbol{v} \, dl - \int_{\Gamma} P v_n \, dS$$ external loads

$$\boxed{\mathcal{R} = \frac{d\mathcal{F}}{dt} + \mathcal{D} + \mathcal{P} + \mathcal{P}_e}$$

Ouzeri et al., bioRxiv., 2025

Governing equations

Minimization of $\mathcal{R}(X;V) = D_X\mathcal{F}(X)\cdot P(X)V + \mathcal{D}(X;V) + \mathcal{P}(X;V)$

Momentum balance in tangential direction

$$\partial_{\boldsymbol{v}}\mathcal{R} = 0 \longrightarrow \begin{cases} \nabla\cdot\boldsymbol{\sigma} = 0 \text{ on } \Gamma \\ \boldsymbol{t} = \boldsymbol{\sigma}\boldsymbol{n} \text{ on } \partial\Gamma_N \end{cases}$$

$\boldsymbol{\sigma} = \boldsymbol{\gamma} + \boldsymbol{\sigma}_e$ active + elastic tension

Momentum balance in normal direction

$$\partial_{v_n}\mathcal{R} = 0 \longrightarrow \boldsymbol{\sigma} : \boldsymbol{k} = P \text{ on } \Gamma$$

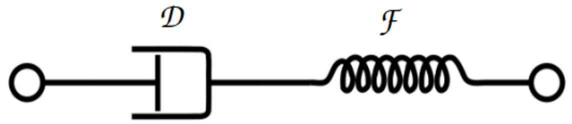
Evolution rule for rate of change of metric

$$\partial_{\dot{G}^{\alpha\beta}}\mathcal{R} = 0 \longrightarrow \dot{G}^{\alpha\beta} = -\frac{1}{2\varrho_0\eta}G^{\alpha\gamma}C_{\gamma\delta}S_e^{\delta\beta}$$

Assuming Neo-hokkean material

Multidimensional extension of Maxwell model :

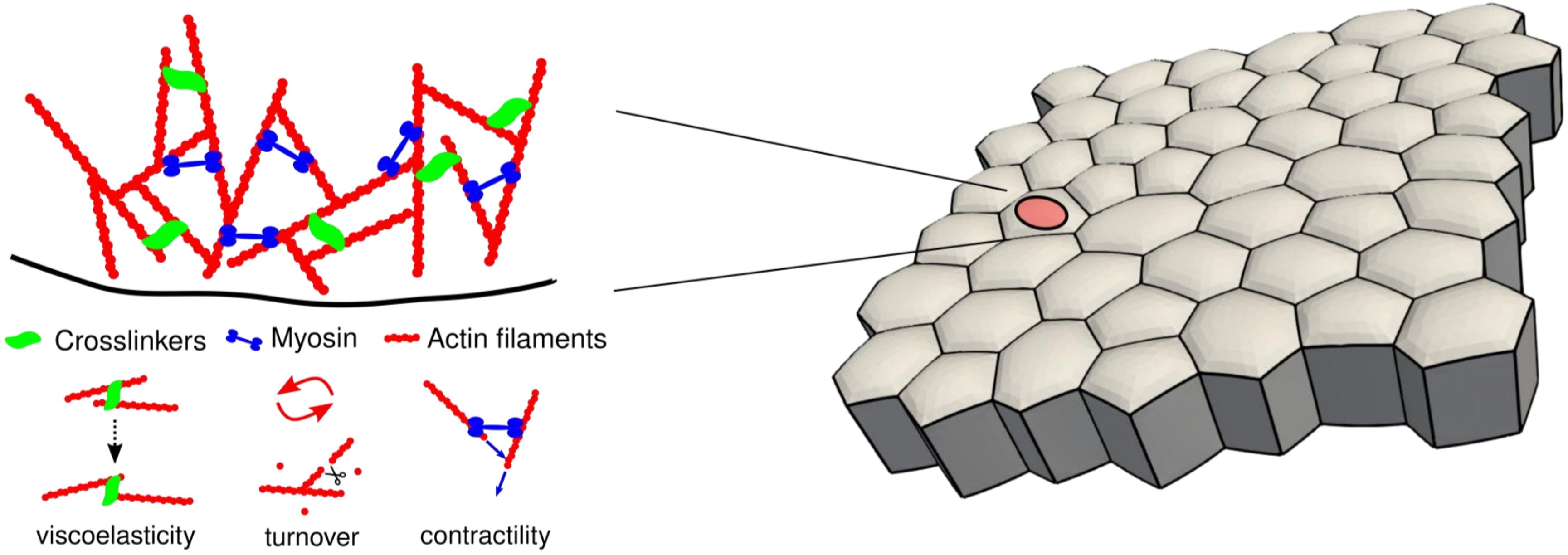
- Very short timescale : active hyperelastic behaviour
- Longer timescales : active viscoelastic behaviour



$$\boxed{\tau_r = \frac{\eta}{\mu}} \qquad \boxed{\tau_t = \frac{1}{k_d}}$$

Ouzeri et al., bioRxiv., 2025

Tissues as a collection of active gels



Cell level

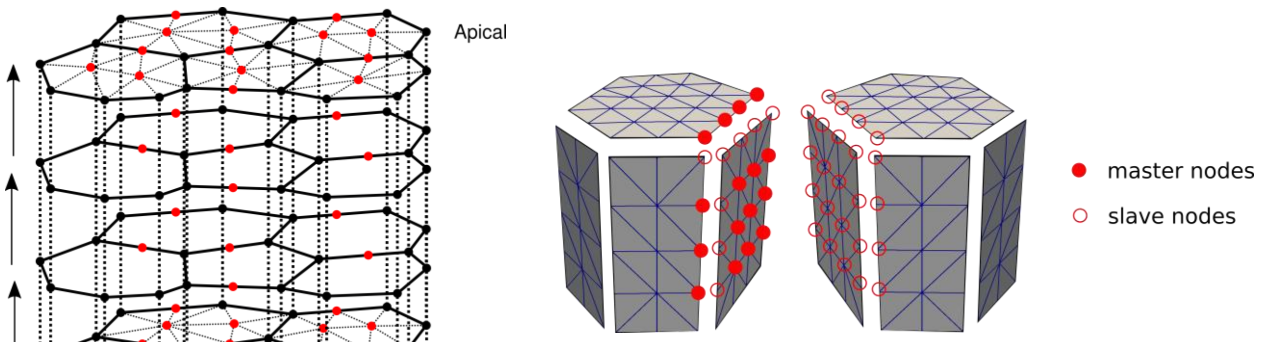
$$\mathcal{L}_c(X_c; V_c, P_c) = \mathcal{R}_c(X_c; V_c) - P_c\dot{\Omega}_c$$

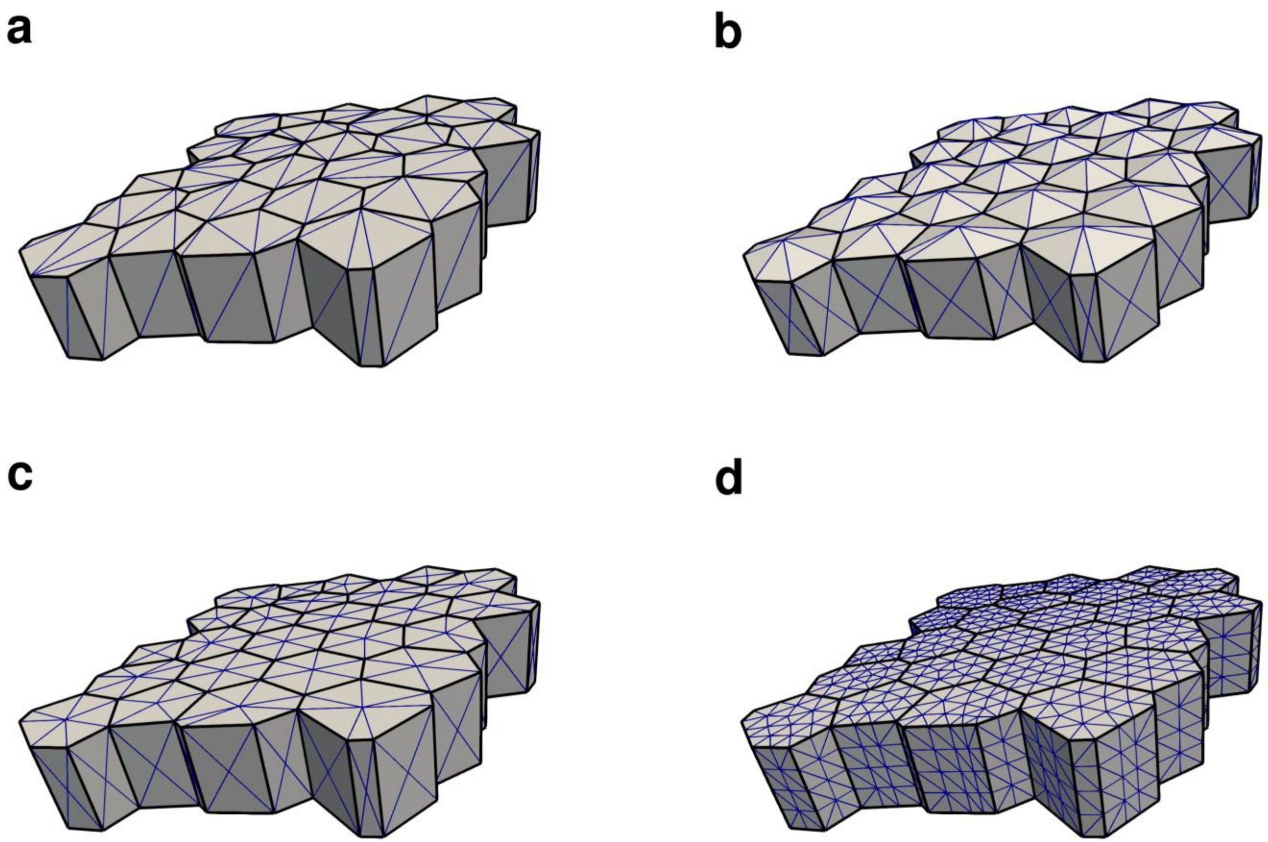
Tissue level

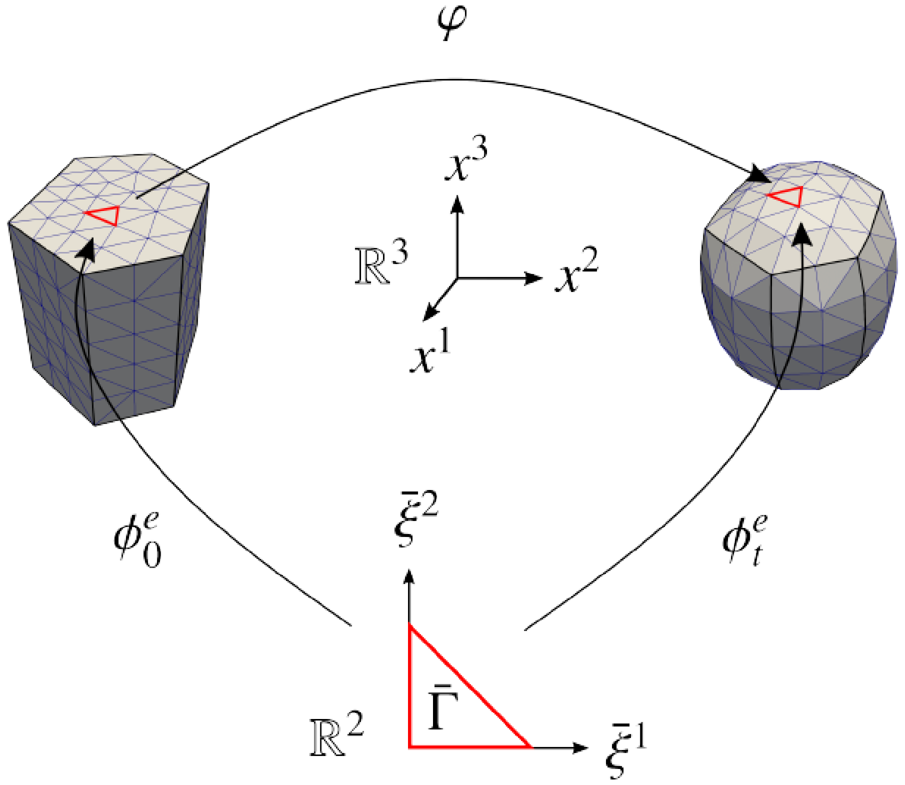
$$\mathcal{L}_m(X_m; V_m, \lambda_m) = \sum_{c \in \langle t \rangle} \mathcal{L}_c(X_c; V_c, P_c)$$

Ouzeri et al., bioRxiv., 2025
Ouzeri, PhD thesis, 2023

Mesh generation and finite element discretization







Ouzeri, PhD thesis, 2023

implicit backward-Euler variational integrator

$$\boldsymbol{V}_I^{n+1} \approx \frac{\mathbf{x}_I^{n+1} - \mathbf{x}_I^n}{\Delta t^n} \qquad \dot{\boldsymbol{G}}_{f,c}^{n+1} \approx \frac{\boldsymbol{G}_{f,c}^{n+1} - \boldsymbol{G}_{f,c}^n}{\Delta t^n}$$

$$\dot{\mathcal{F}}_{f,c}\left[\phi, \rho_{f,c}, \boldsymbol{G}_{f,c}; \boldsymbol{V}, \dot{\boldsymbol{G}}_{f,c}\right] \approx \frac{1}{\Delta t^n}\mathcal{F}_{f,c}\left[\left\{\mathbf{x}_I^{n+1}, \boldsymbol{G}_{f,c}^{n+1}\right\}\right]$$

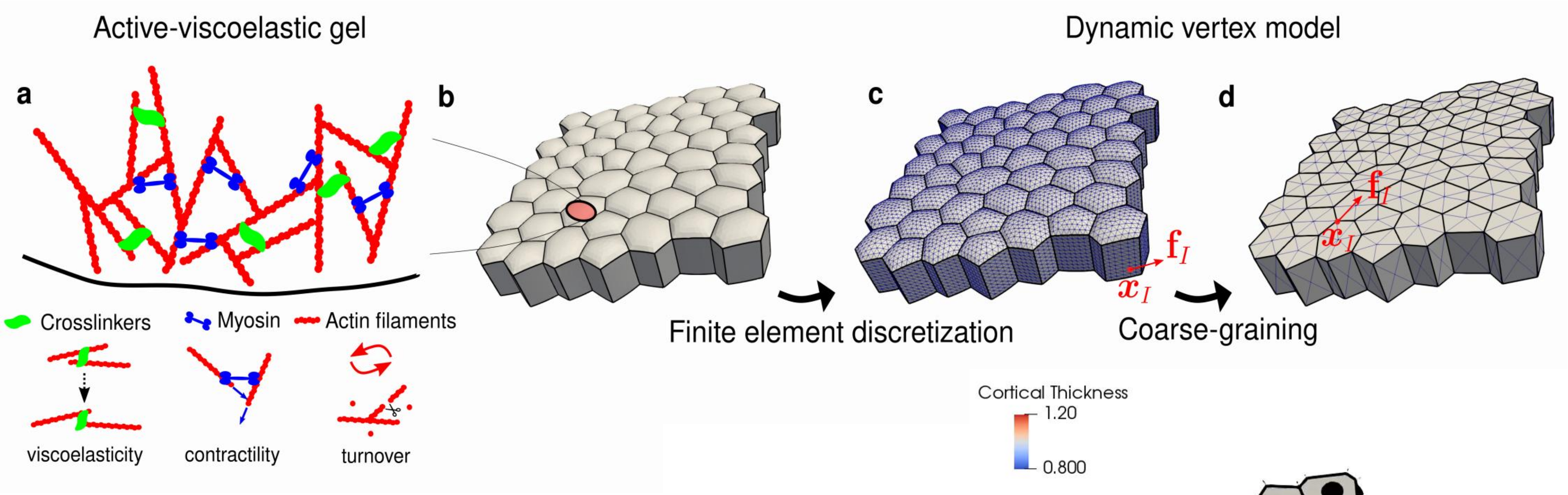
$$\mathcal{D}_{f,c}\left[\phi, \rho_{f,c}, \boldsymbol{G}_{f,c}; \dot{\boldsymbol{G}}_{f,c}\right] \approx \mathcal{D}_{f,c}\left[\left\{\mathbf{x}_I^n, \boldsymbol{G}_{f,c}^n, \rho_{f,c}^n\right\}; \left\{\frac{\boldsymbol{G}_{f,c}^{n+1} - \boldsymbol{G}_{f,c}^n}{\Delta t^n}\right\}\right]$$

$$\mathcal{P}_{f,c}\left[\phi, \rho_{f,c}; \boldsymbol{V}\right] \approx \mathcal{P}_{f,c}\left[\left\{\mathbf{x}_I^n, \rho_{f,c}^n\right\}; \left\{\frac{\mathbf{x}_I^{n+1} - \mathbf{x}_I^n}{\Delta t^n}\right\}\right]$$

$$P_c\dot{\Omega}_c \approx P_c^{n+1}\frac{\Omega_c\left(\left\{\mathbf{x}_I^{n+1}\right\}\right) - \Omega_c\left(\left\{\mathbf{x}_I^n\right\}\right)}{\Delta t^n}$$

Torres-Sánchez et al., JFM, 2019
Ouzeri, PhD thesis, 2023

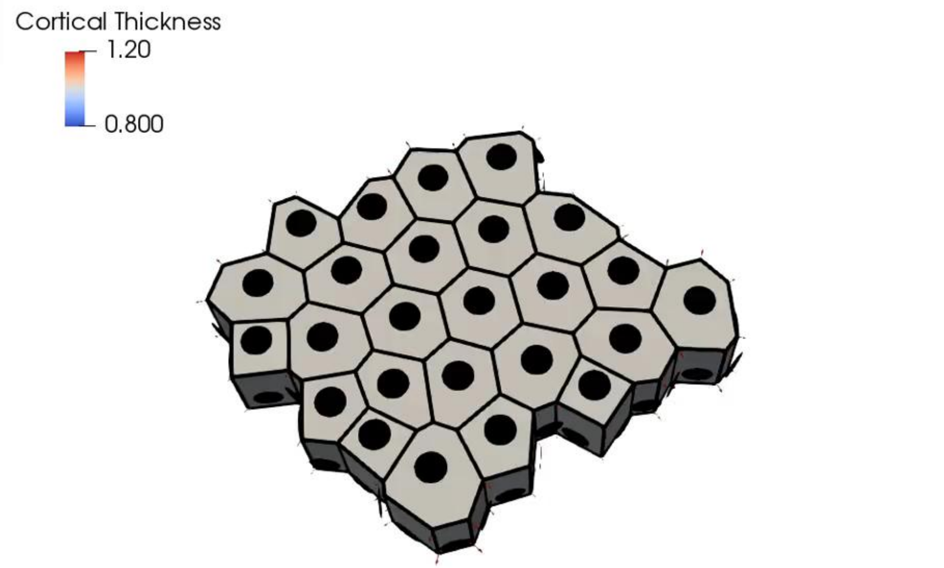
Discrete governing equations



$$\left\{ \begin{aligned} & \rho_{f,c}^{n+1} - \rho_{f,c}^{n} - \Delta t^{n} \left[k_p C_0 - \rho_{f,c}^{n+1} \left(\frac{J_{f,c}^{n+1}}{J_{f,c}^{n}} + k_d \right) \right] = 0 \\ & \left\{ \mathbf{x}_I^{n+1}, \boldsymbol{G}_{f,c}^{n+1}, P_c^{n+1} \right\} = \underset{\{\mathbf{x}_I, \boldsymbol{G}_{f,c}\}}{\arg\min} \, \underset{P_c}{\arg\max} \left(\mathcal{L}_m \left[\left\{ \mathbf{x}_I^{n}, \rho_{f,c}^{n}, \boldsymbol{G}_{f,c}^{n} \right\}; \left\{ \mathbf{x}_I, \boldsymbol{G}_{f,c} \right\}, \left\{ P_c \right\} \right] \right) \end{aligned} \right.$$

Solving an active gel on each curved face of each cell

hiperlife



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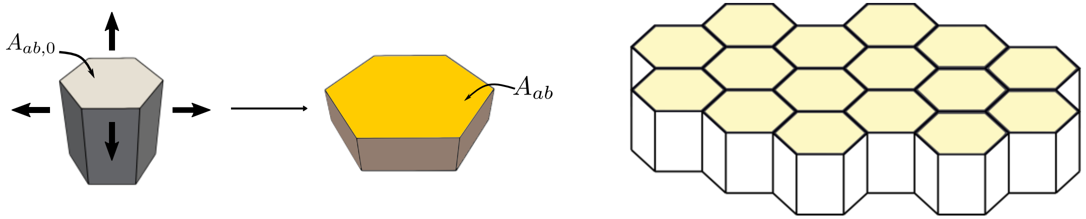
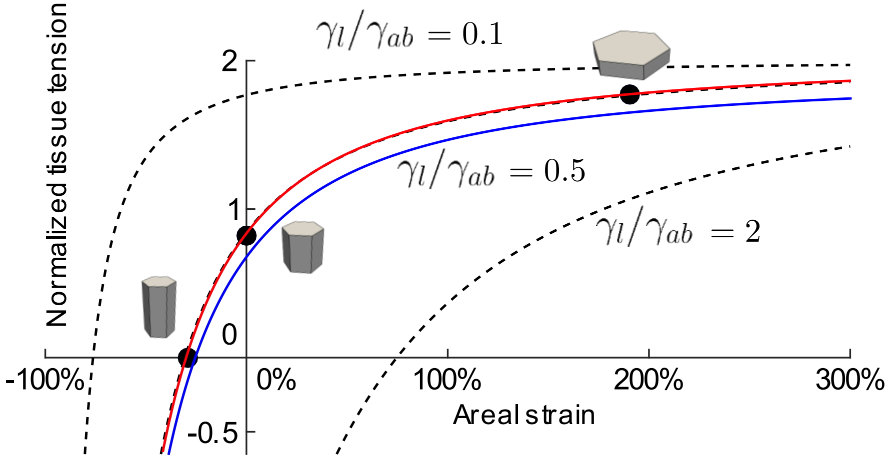
Ouzeri et al., bioRxiv., 2025
Ouzeri, PhD thesis, 2023

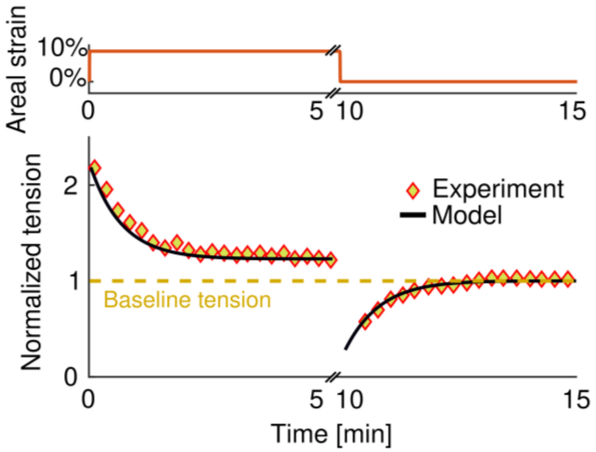
Tissue response under stretch

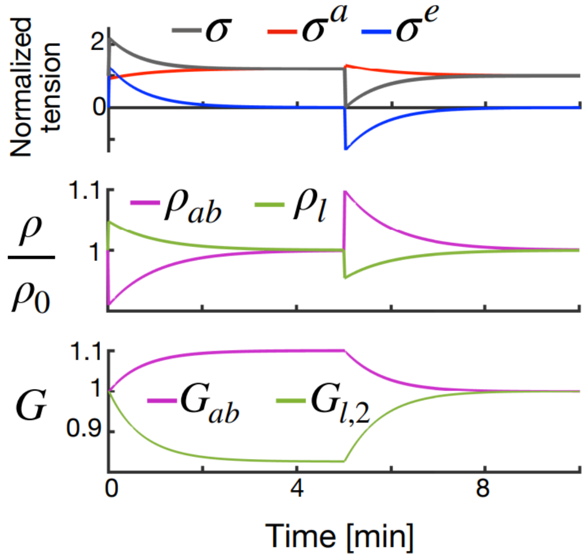


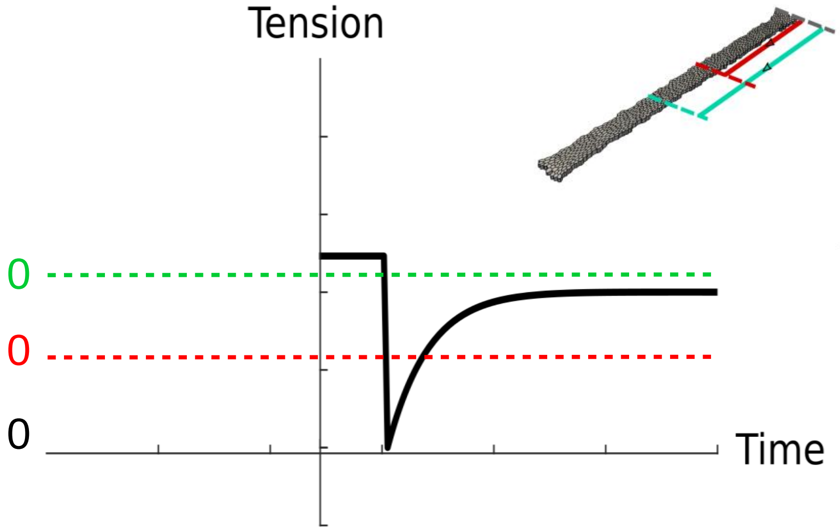


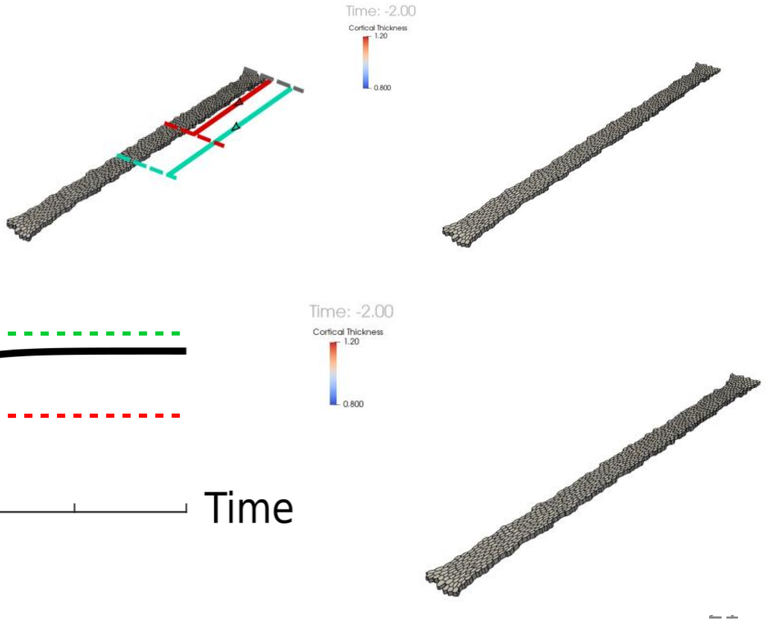
$$\sigma = 2 - \frac{\xi_l}{\xi_{ab}} \frac{k}{(\varepsilon_{ab}+1)^{3/2}}$$

$$\varepsilon_{ab} = \frac{A_{ab}}{A_{ab,0}} - 1$$



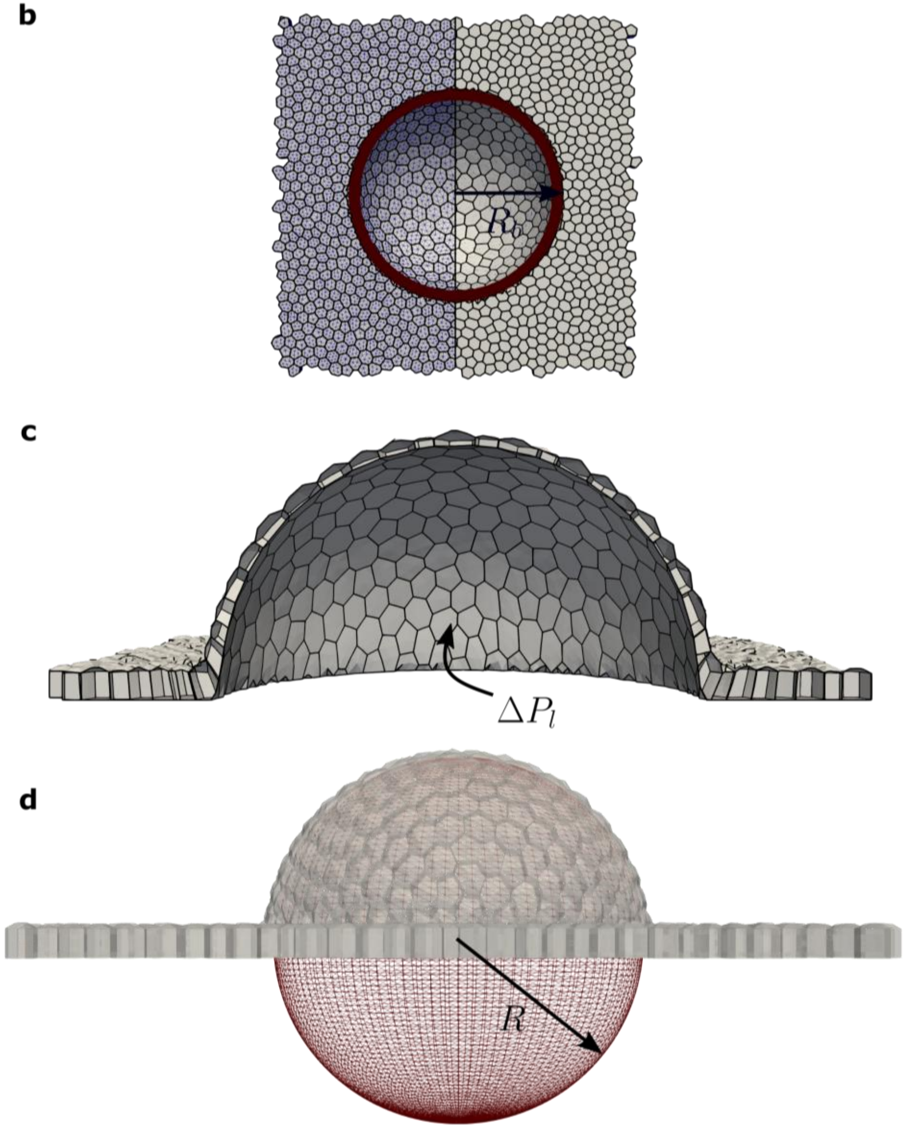


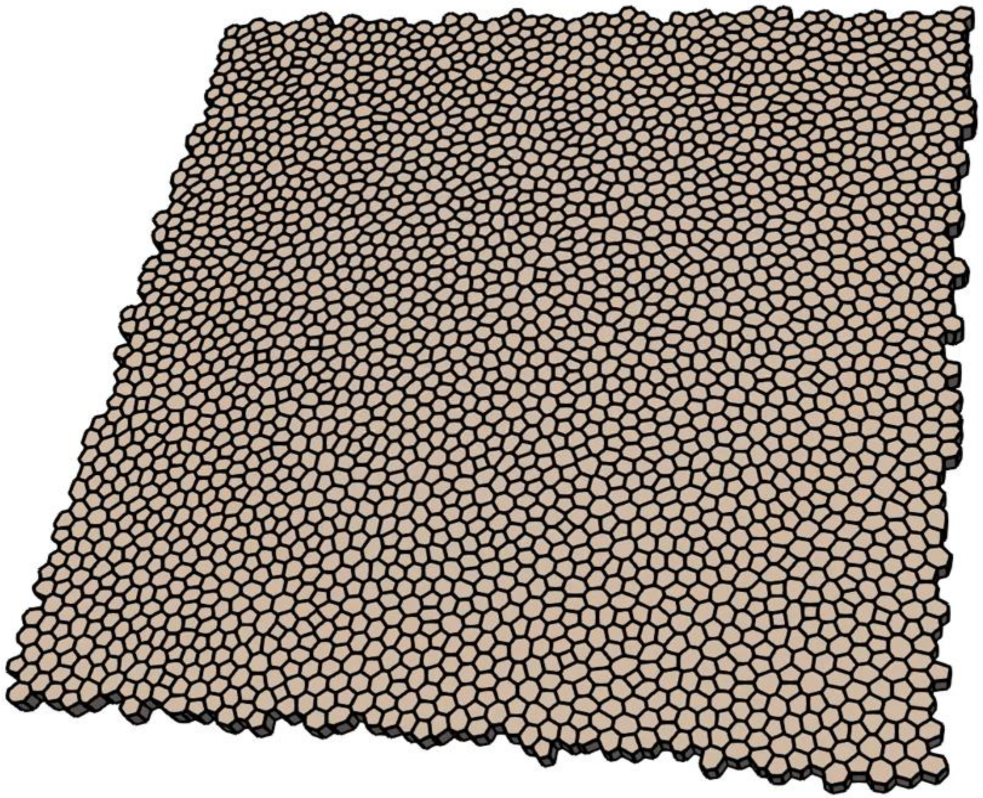




Ouzeri et al., bioRxiv., 2025

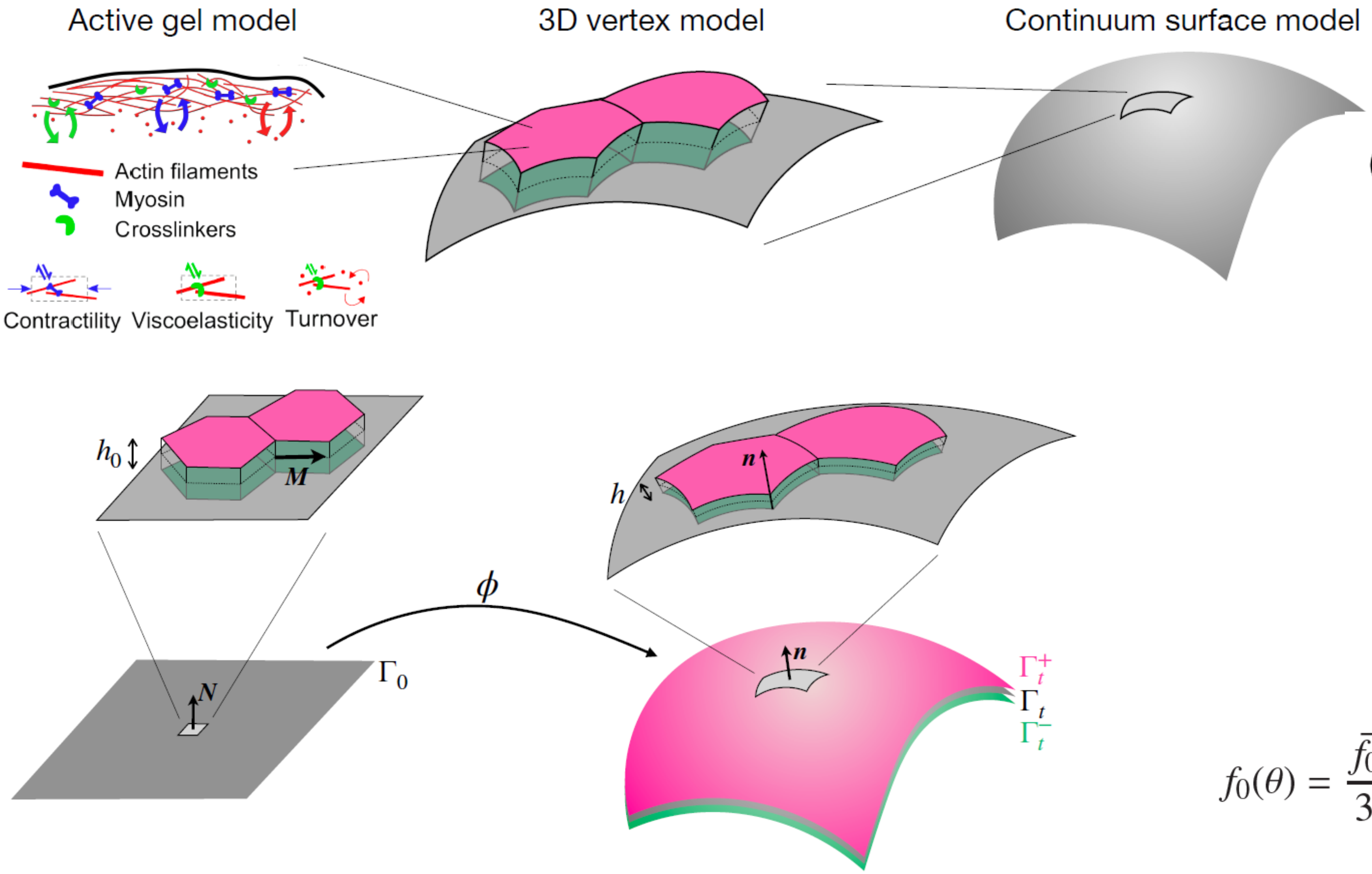
Mechanics of epithelial domes : CVM

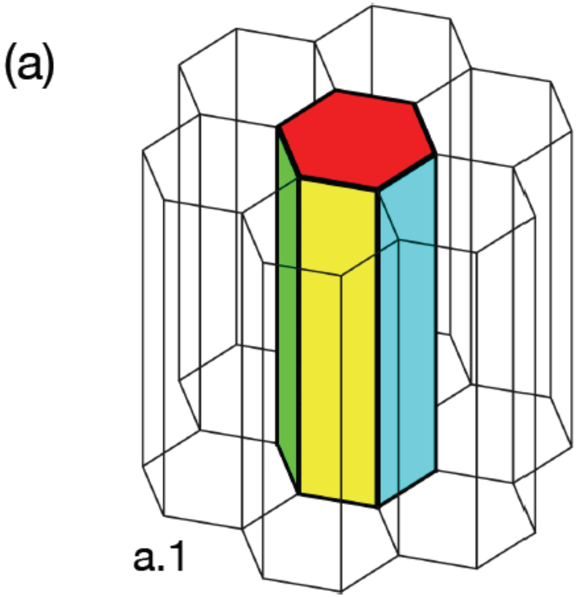




Marín-Llauradó et al., Nat. Commun., 2023

Continuum Kirchhoff theory for epithelial shells





$$\int_{\Gamma_0}\int_0^{\pi} f_0(\boldsymbol{X},\theta)\,d\theta\,dS_0$$

$$f_0(\theta)=\frac{\bar{f}_0}{3}\left[\delta(\theta)+\delta\left(\theta-\frac{\pi}{3}\right)+\delta\left(\theta-\frac{2\pi}{3}\right)\right]$$

$$\bar{f}_0=\frac{2\sqrt{3}}{3}\frac{h_0}{\ell_0}$$

Bal et al., bioRxiv., 2025

Continuum Kirchhoff theory for epithelial shells

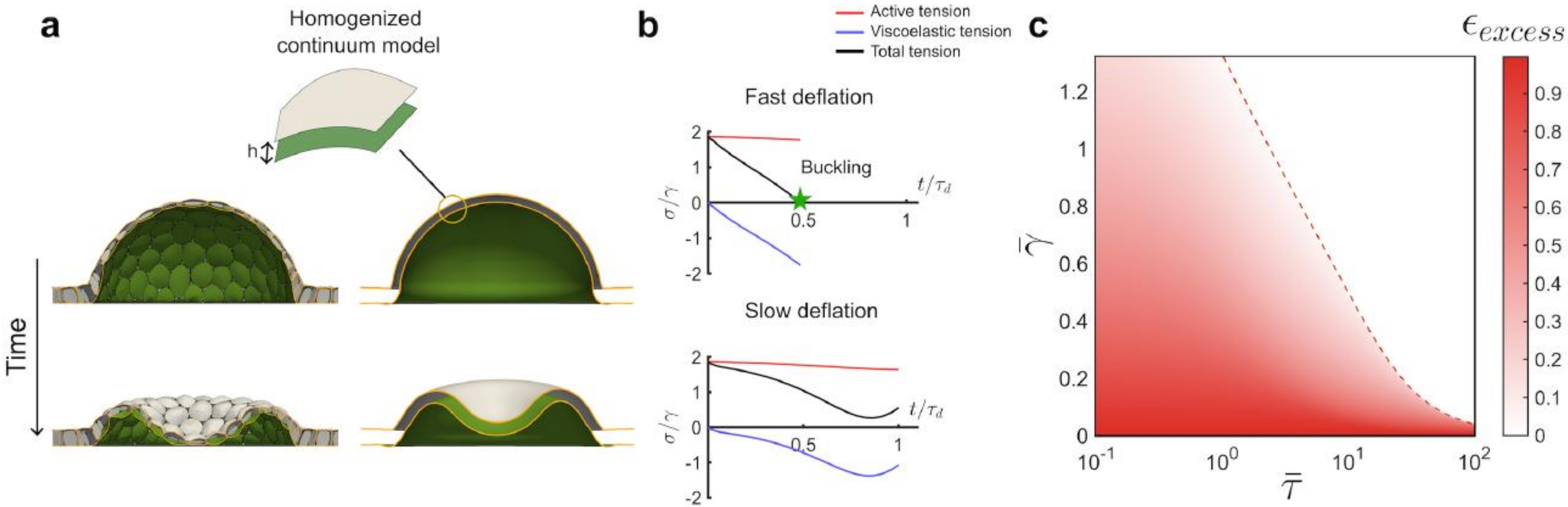
$$
\begin{aligned}
\mathcal{R}[\dot{\varphi}, \dot{\mathbb{G}}^{\pm}, \dot{\mathbb{G}}^{\mathrm{L}}] = {} & \int_{\Gamma_0} \left[\frac{1}{2} \boldsymbol{S}^{\mathrm{eff}} : \dot{\boldsymbol{C}} + \boldsymbol{m}^{\mathrm{eff}} : \dot{\boldsymbol{k}} \right] dS_0 + \int_{\Gamma_0} \frac{\tilde{\eta}_{\mathrm{m}}}{2} |\boldsymbol{V}|^2 J^{\mathrm{mid}} dS_0 \\
& + \int_{\Gamma_0} \left[\sum_{\alpha=\pm} \left(\frac{\partial \Psi^{\alpha}}{\partial \mathbb{G}^{\alpha}} : \dot{\mathbb{G}}^{\alpha} + \Phi^{\alpha}(\dot{\mathbb{G}}^{\alpha}) \right) \varrho_0^{\alpha} \frac{G^{\alpha}}{G} + \int_0^{\pi} \left(\frac{\partial \Psi^{\mathrm{L}}}{\partial \mathbb{G}^{\mathrm{L}}} : \dot{\mathbb{G}}^{\mathrm{L}} + \Phi^{\mathrm{L}}(\dot{\mathbb{G}}^{\mathrm{L}}) \right) \varrho_0^{\mathrm{L}} f_0(\theta) d\theta \right] dS_0,
\end{aligned}
$$

$$
\boldsymbol{S}^{\mathrm{eff}} = \boldsymbol{S}^{+} + \boldsymbol{S}^{-} + \frac{h}{4} \left[(\boldsymbol{S}^{+} + \boldsymbol{S}^{-}) : \boldsymbol{k} \right] \boldsymbol{C}^{-1} + \int_0^{\pi} \left(S^{\mathrm{L}}_{MM} \boldsymbol{M} \otimes \boldsymbol{M} - \frac{1}{{J^{\mathrm{mid}}}^2} S^{\mathrm{L}}_{NN} \boldsymbol{C}^{-1} \right) f_0(\theta) d\theta
$$

$$
\boldsymbol{m}^{\mathrm{eff}} = -\frac{h}{4} (\boldsymbol{S}^{+} - \boldsymbol{S}^{-})
$$

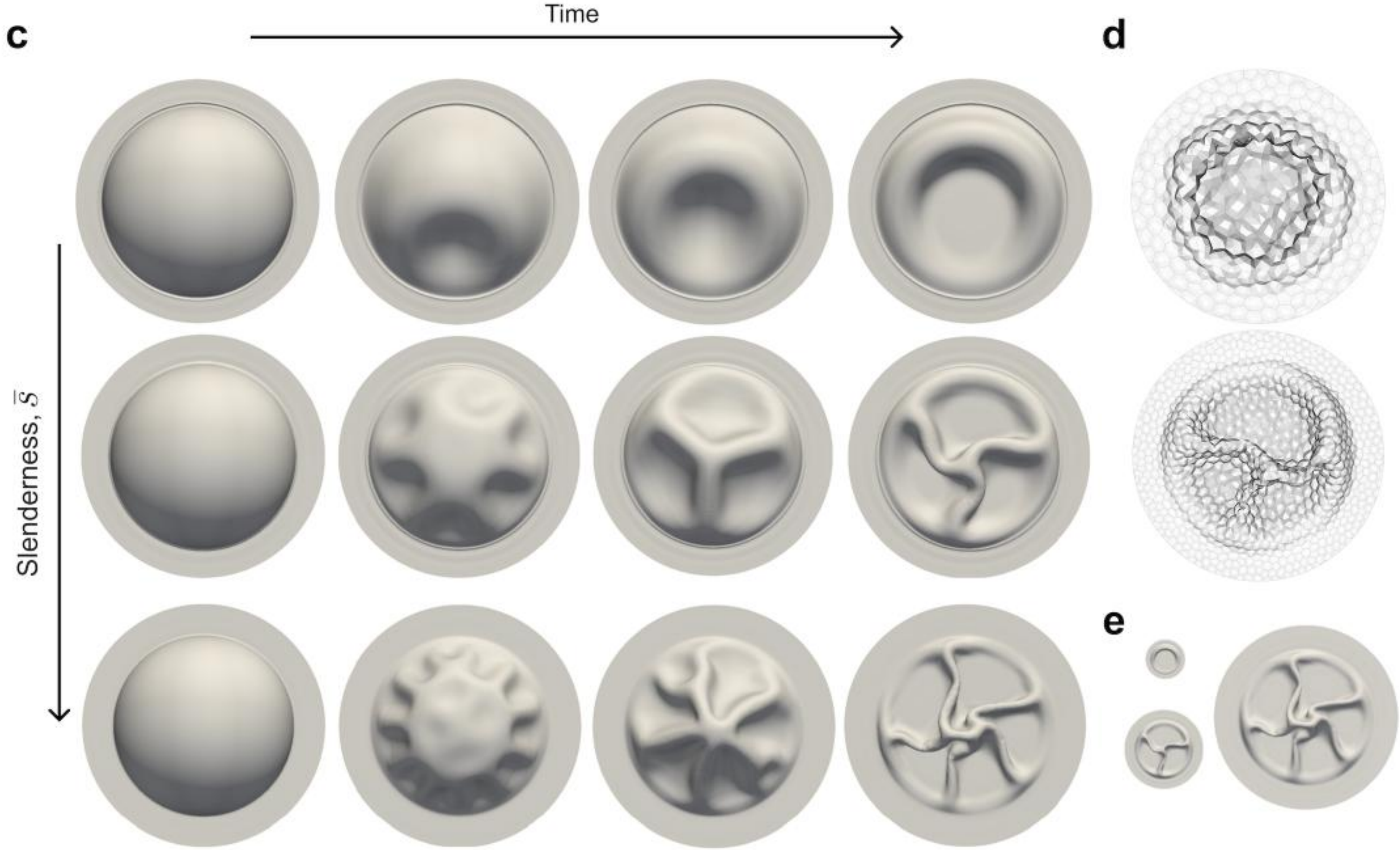
Bal et al., bioRxiv., 2025

Buckling phase diagram



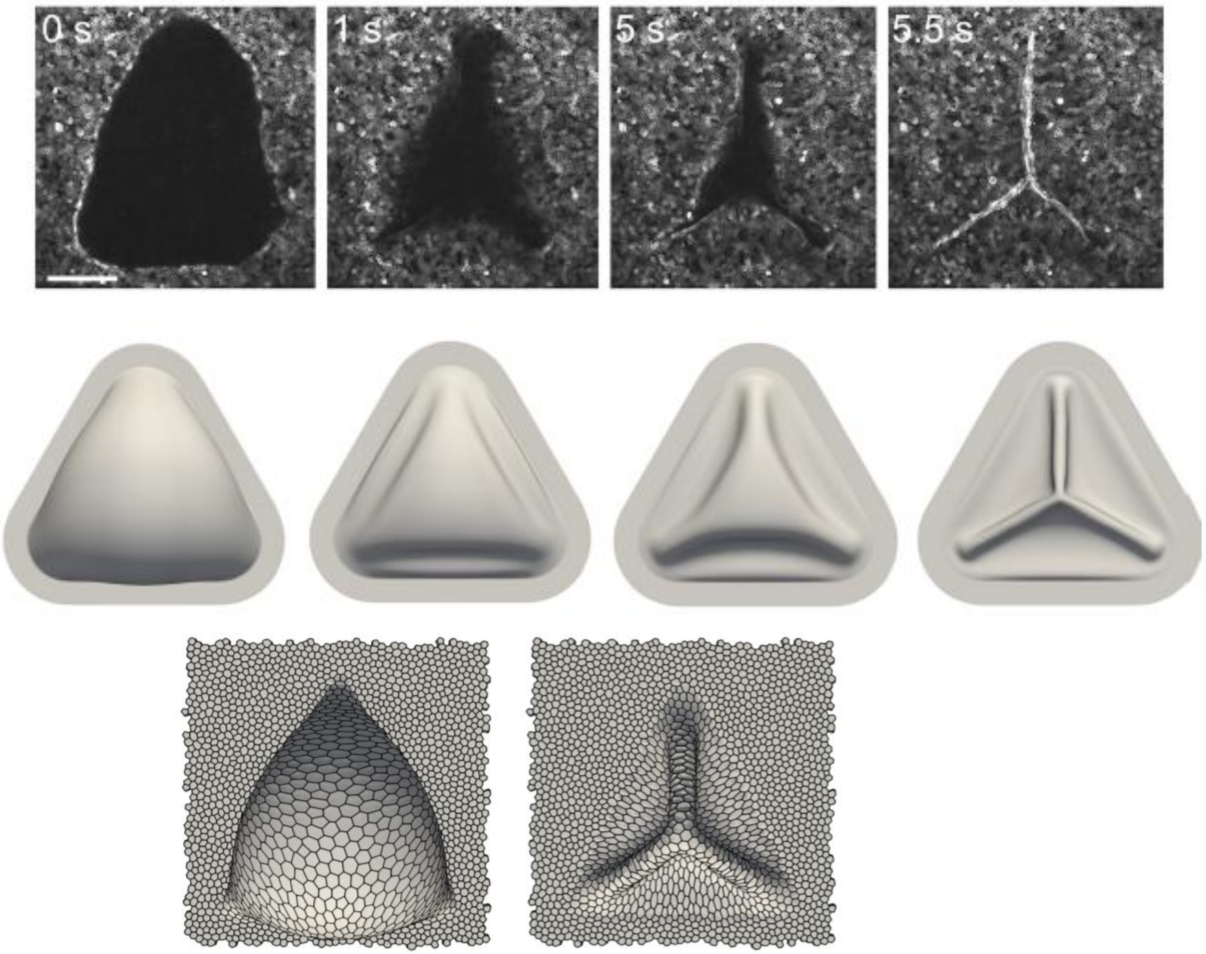
Charahe et al., bioRxiv., 2025

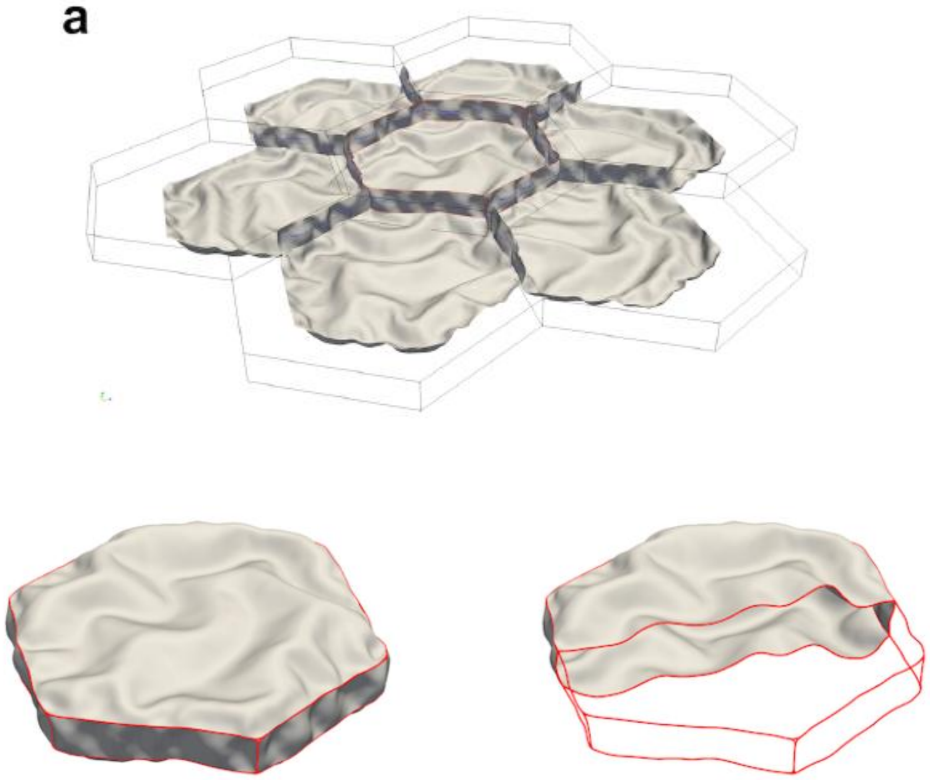
Symmetry breaking and wrinkle-to-fold transition



Charahe et al., bioRxiv., 2025

Engineering folds





Charahe et al., bioRxiv., 2025

Conclusion and further work

- Established mechanical rules for unsupported epithelial buckling (intrinsic mechanical properties)
- Explored new regime of buckling dynamics across a broad range of time scales, length scales, geometries, and mechanical properties of the epithelium
- Rational design of folds
- Epithelial buckling as a stress-buffering and morphogenetic mechanism

- Analytical arguments for active wrinkles and folds
- “Geometrical morphogens”

Collaborators

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Thank you for your attention

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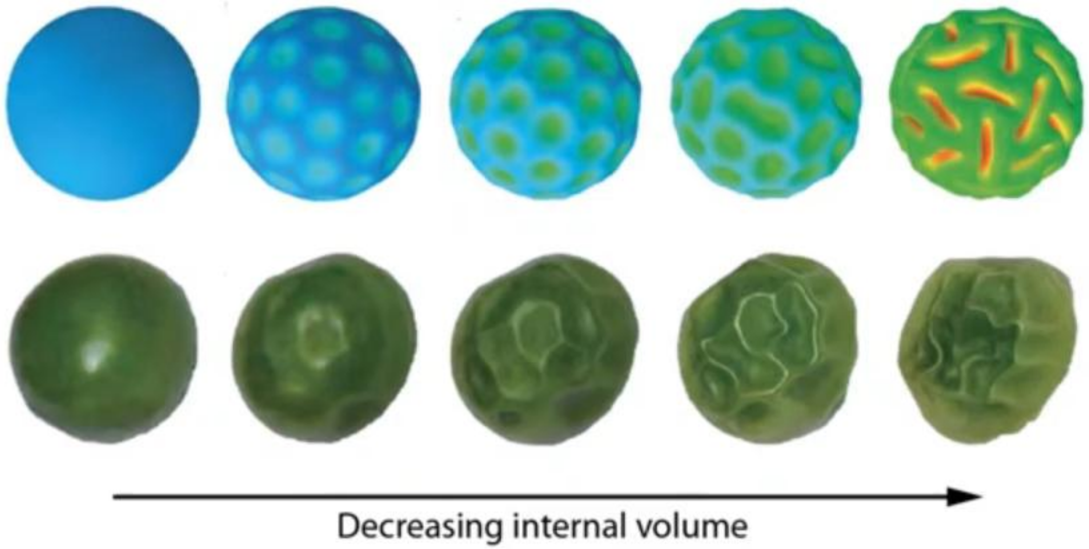
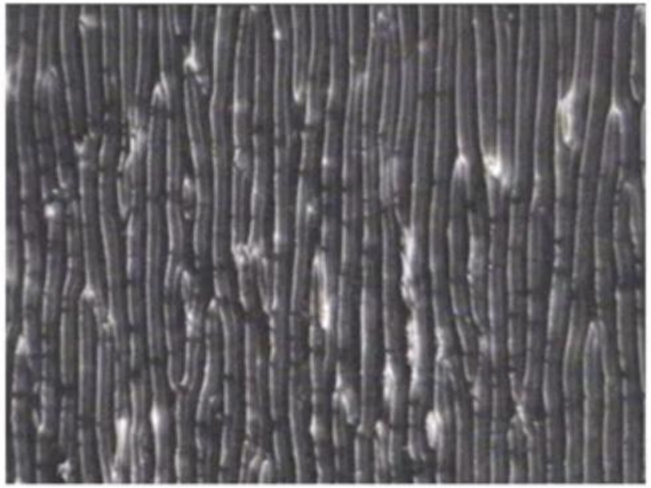
Extra slides

Three types of wrinkles

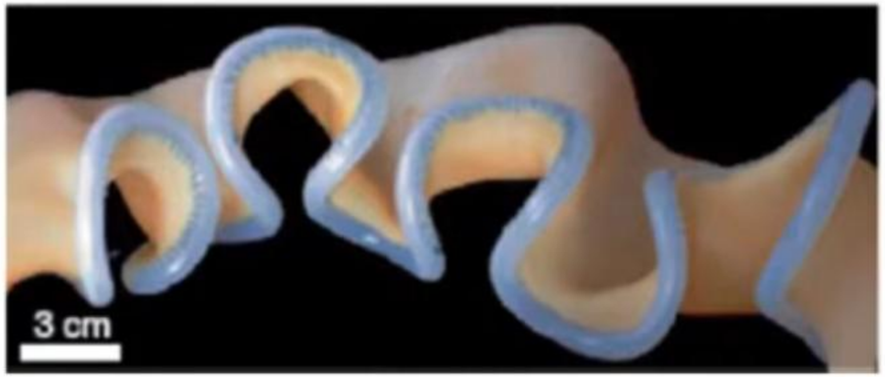
- Three ways wrinkles arise
  - Constrained volume change
  - Hard and soft layers
  - Mismatched deformation systems

Images below: Li, Bo, Yan-Ping Cao, Xi-Qiao Feng, and Huajian Gao. *Soft Matter* 8, no. 21 (2012): 5728-5745





Multilayer system with hard surface layer and soft interior



Orange rubber was stretched then attached to blue rubber

Slide from Alexander K Landauer, Surface Wrinkling: a brief introduction, 2015