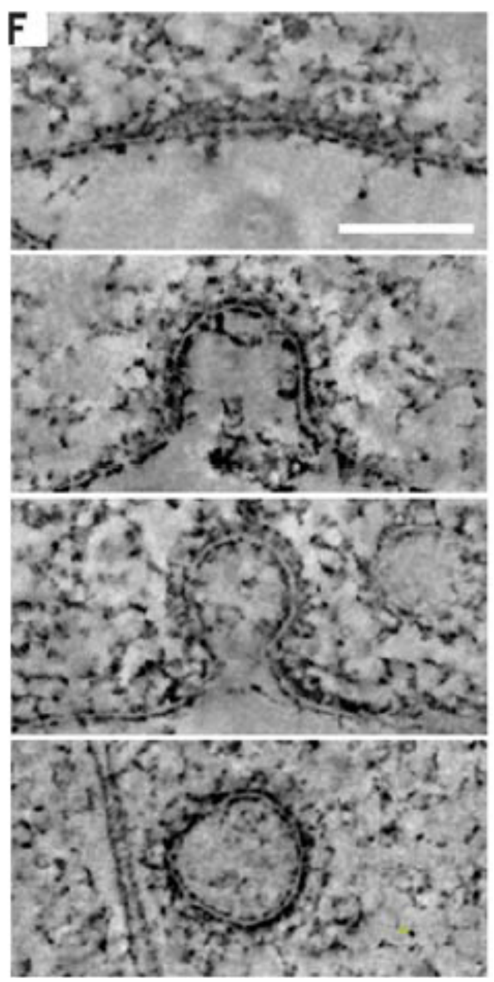
UC San Diego

Interplay between Curvature-inducing Proteins and Intracellular Membrane Structures:

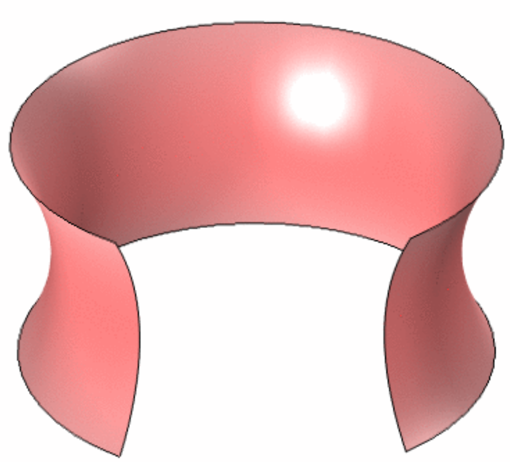
Application to Biologically Relevant Minimal Surfaces

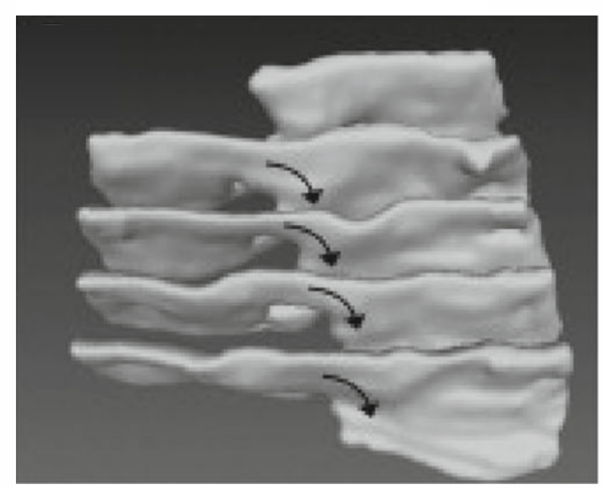
Morgan Chabanon & Padmini Rangamani

Department of Mechanical and Aerospace Engineering
University of California San Diego

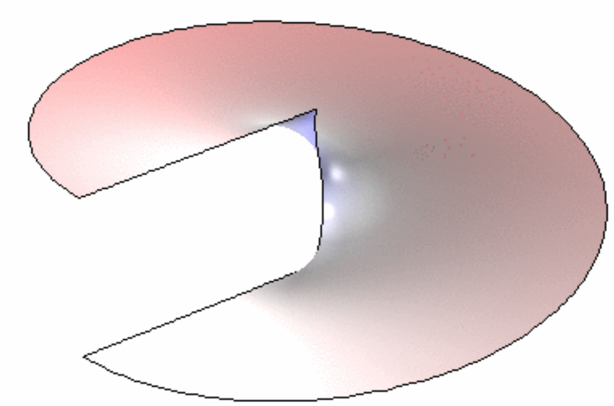


Avinoam et al., Science (2015)





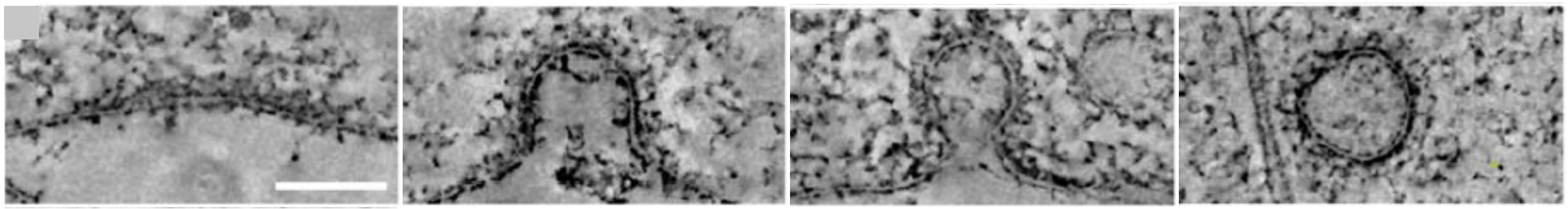
Terasaki et al., *Cell* (2014)



From membrane shape to membrane mechanics

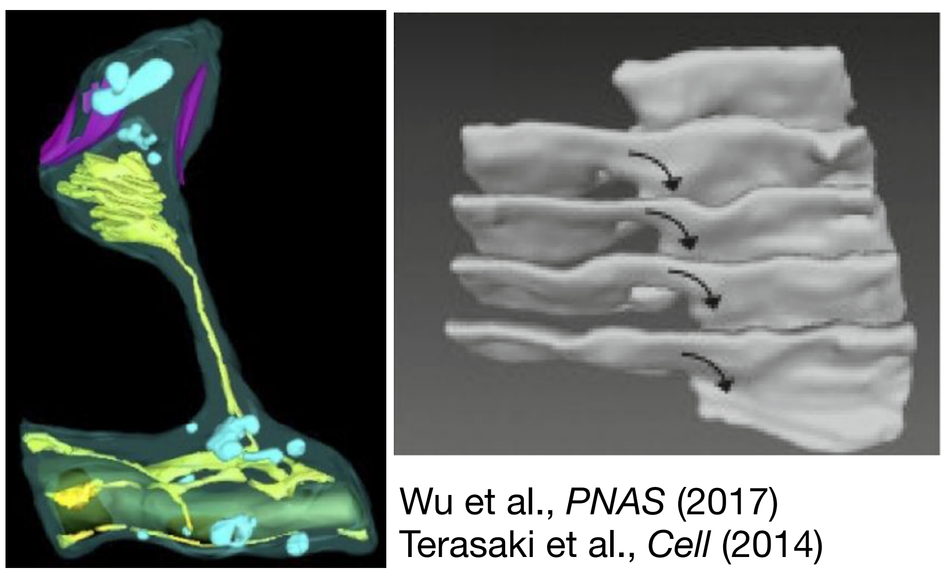
- Large body of experimental data on **membrane geometry**

Clathrin mediated endocytosis



Avinoam et al., Science (2015)

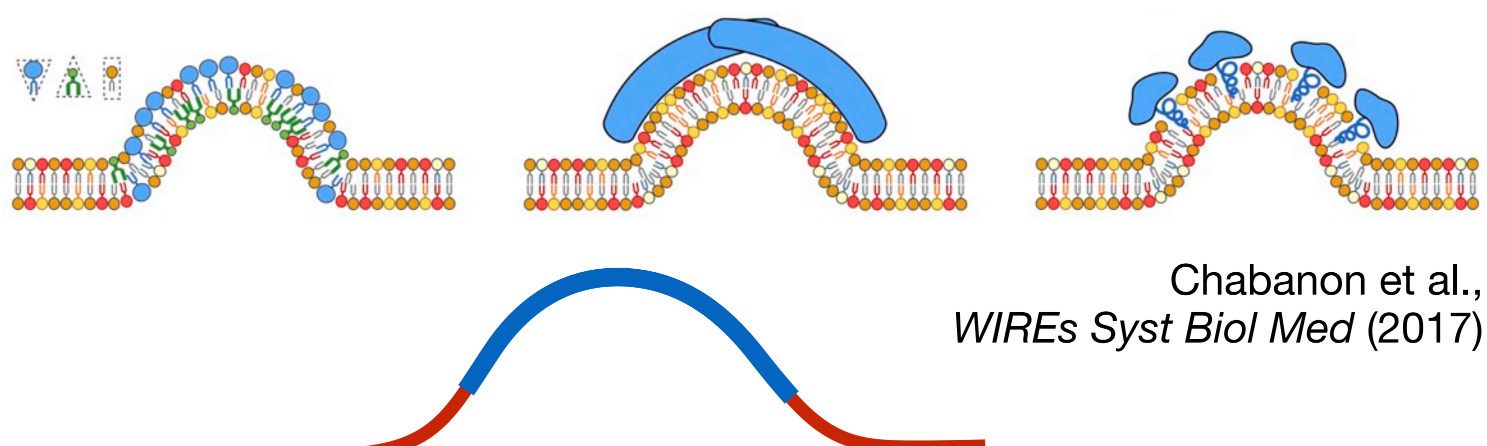
Endoplasmic reticulum



Wu et al., *PNAS* (2017)
Terasaki et al., *Cell* (2014)

What biophysical mechanisms allow cells to shape and maintain observed membrane structures?

- **Spontaneous curvature**
  - Membrane heterogeneity
  - Continuous quantity

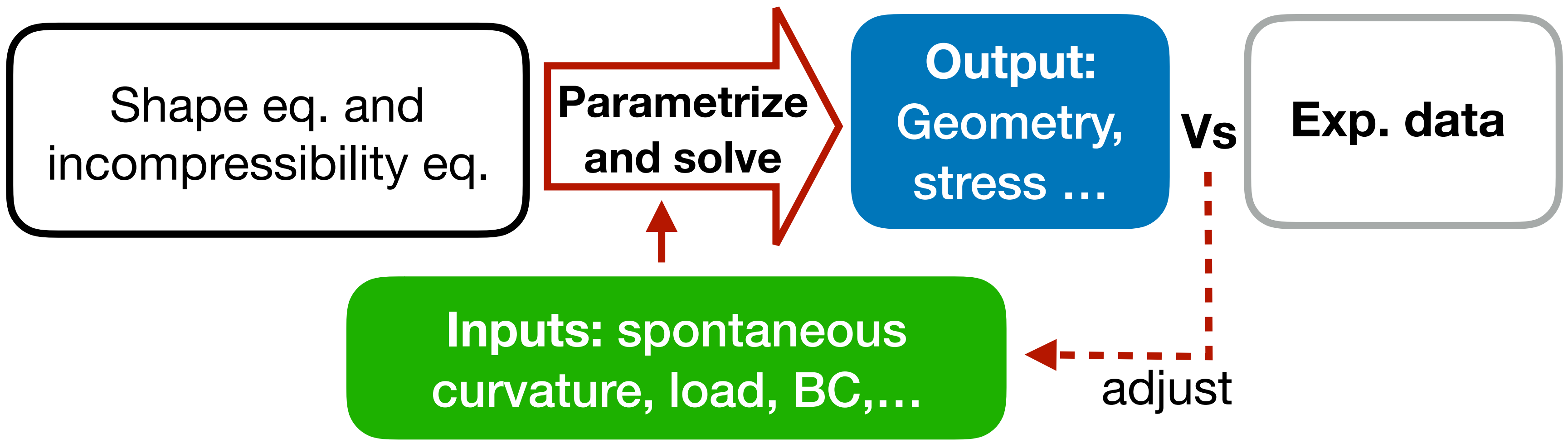


Chabanon et al., *WIREs Syst Biol Med* (2017)

Proposed methodology

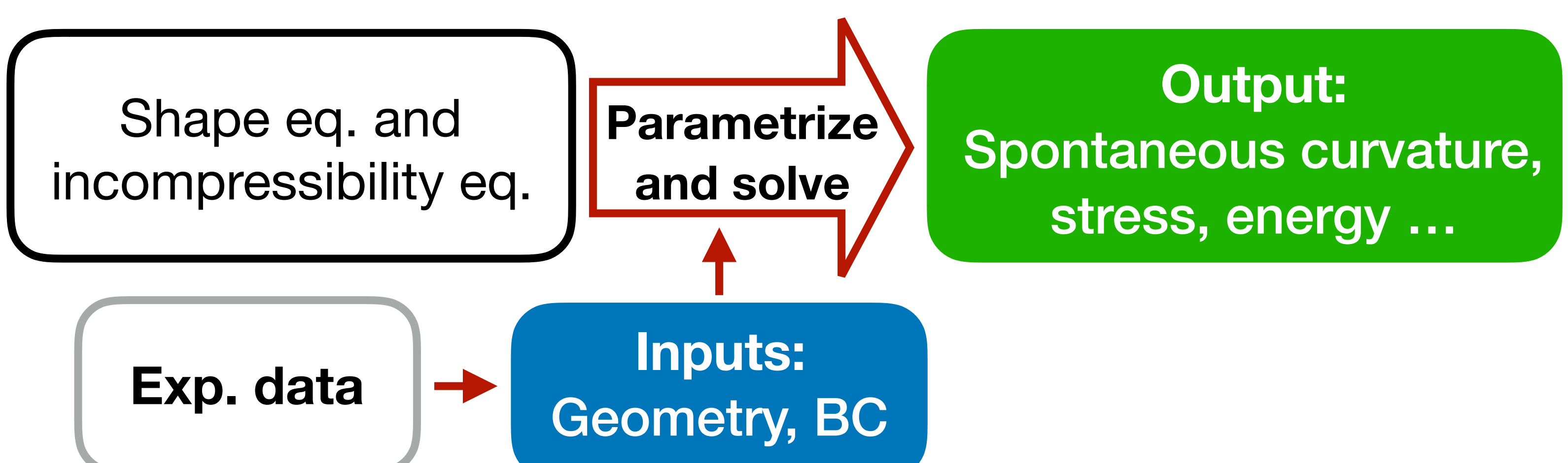
- Classical **continuum approach** to membrane biomechanics at equilibrium

Forward approach



- Inverse approach: use **geometry as an input**, and compute BC, load and/or distribution of **spontaneous curvature**

Inverse approach



Chabanon & Rangamani, *Soft Matter* (2018)
Chabanon & Rangamani, *in preparation*

Modeling approach

Augmented Helfrich energy to account for protein density σ:

$$W(\sigma,H,K;\theta^\alpha) = \underbrace{A(\sigma)}_{\text{protein contribution to membrane energy}} + k(\theta^\alpha)[H - \underbrace{C(\sigma)}_{\text{spontaneous curvature induced by proteins}}]^2 + k_G(\theta^\alpha)K\,,$$

Shape equation

$$\Delta[k(H-C)] + 2H\Delta k_G - (k_G)_{;\alpha\beta}b^{\alpha\beta} + 2k(H-C)(2H^2-K) + 2H(k_G K - W(\sigma,H,K;\theta^\alpha)) = p + 2\lambda H\,.$$

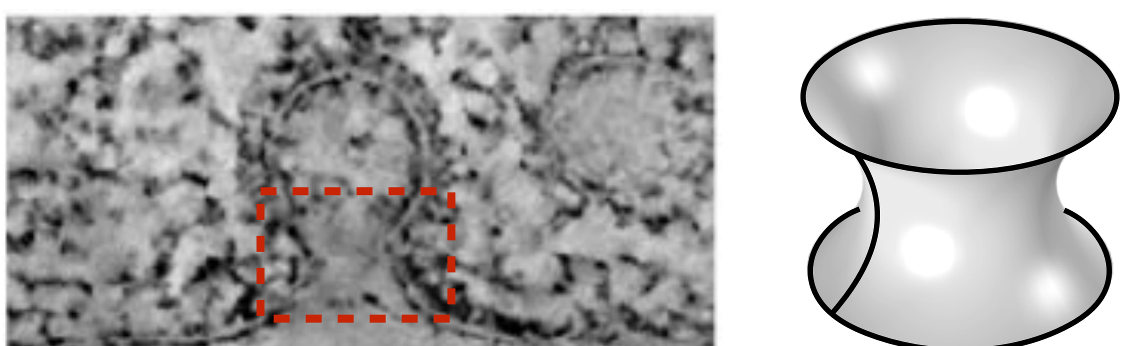
Incompressibility condition

$$\nabla\lambda = -W_\sigma\nabla\sigma - \nabla k(H-C)^2 - \nabla k_G K\,,$$

with $W_\sigma = A_\sigma - 2k(H-C)C_\sigma\,.$

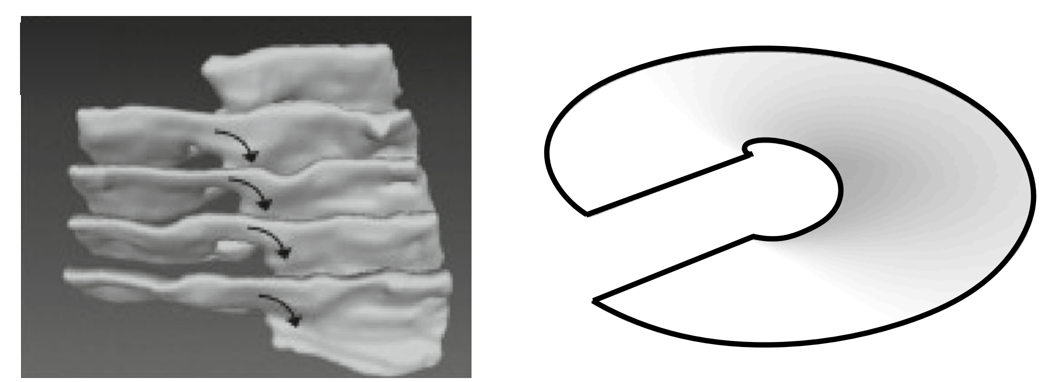
Assumptions on the geometry

Catenoid-like necks



Chabanon & Rangamani, *Soft Matter* (2018)

Helicoidal ramps



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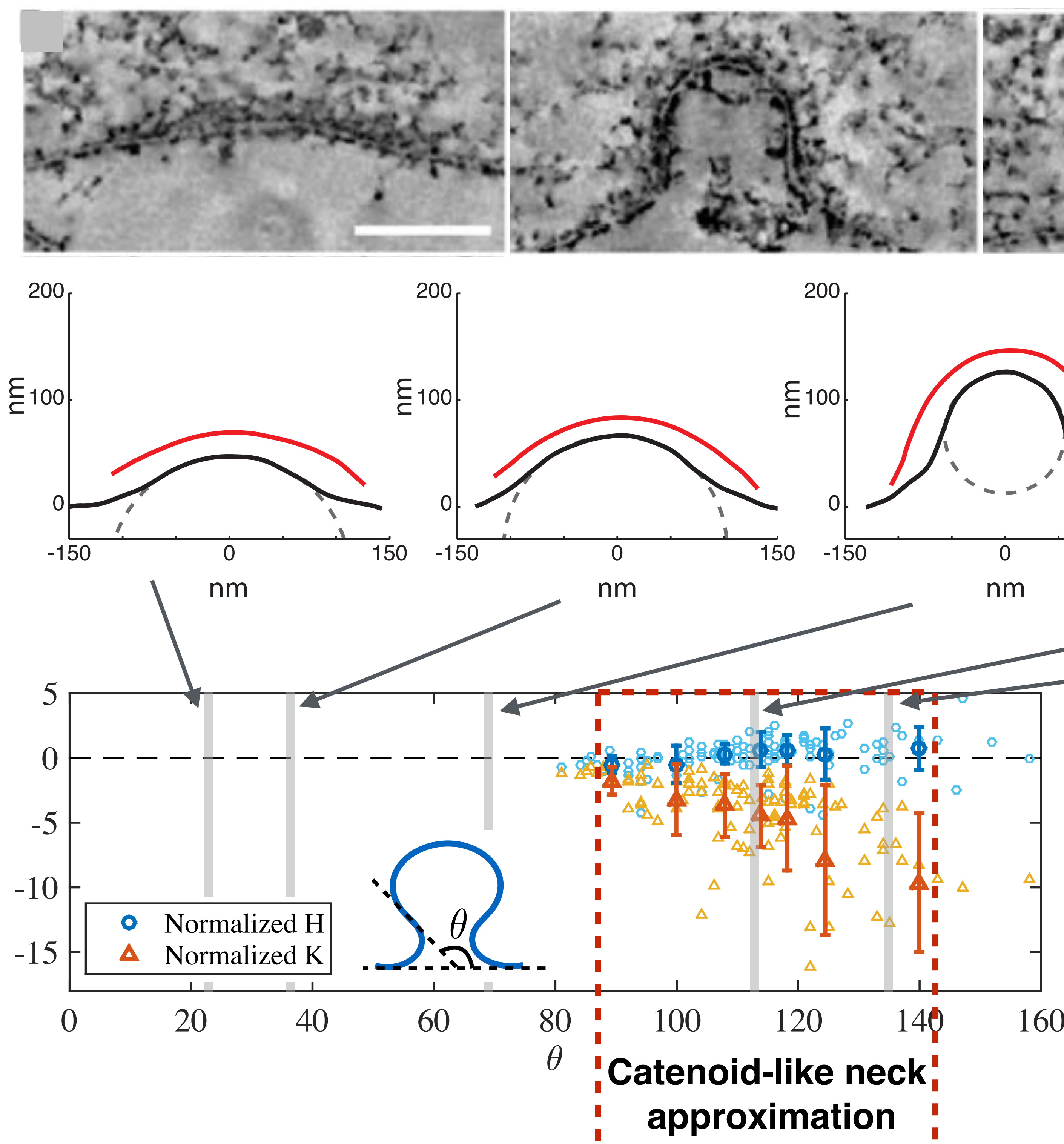
For **minimal surfaces** ($H=0$) with homogeneous mechanical properties

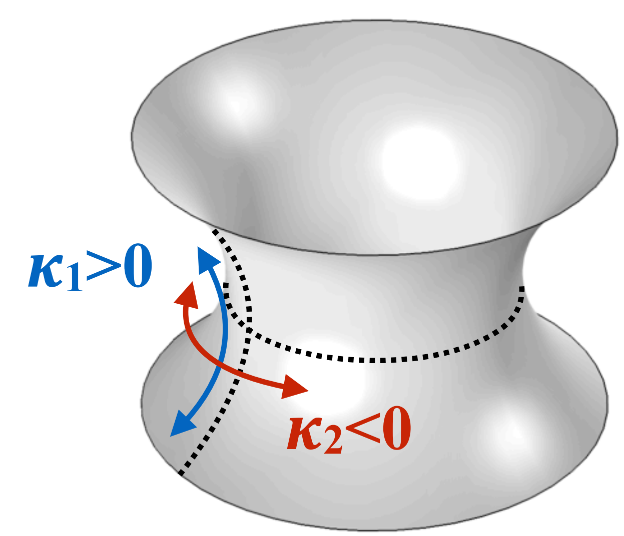
$$\boxed{\Delta C(\sigma) - 2KC(\sigma) = 0} \qquad \lambda = -[A(\sigma) + kC(\sigma)^2] + \lambda_0\,.$$

Imposing the geometry, we solve for the distribution of spontaneous curvature (C), and compute the total bending energy

Necks as catenoids

Avinoam, et al., *Science* (2015)





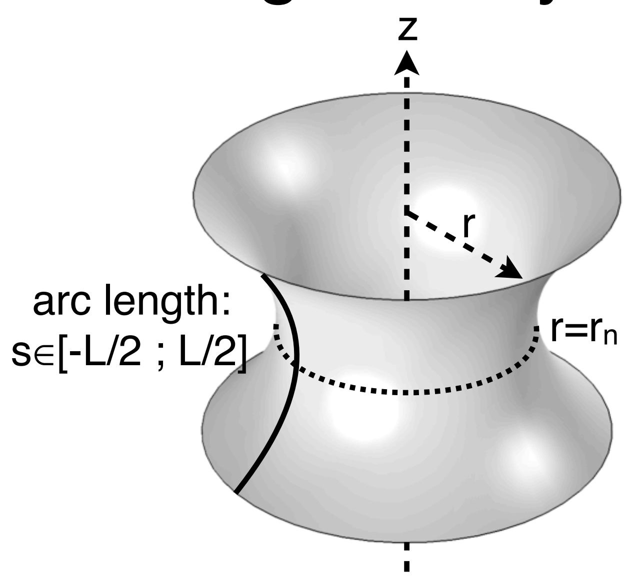
$$H = (\kappa_1 + \kappa_2)/2$$
$$K = \kappa_1 \kappa_2$$

Catenoid:
$H = 0$ and $K < 0$

Chabanon & Rangamani, *Soft Matter* (2018)

Application to catenoids

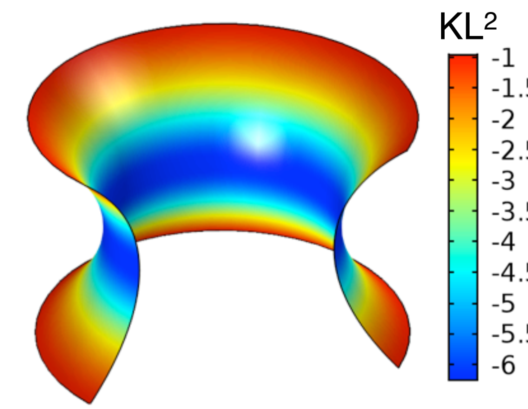
- **Catenoid** geometry $r = r_n \cosh(z/r_n) \quad \text{with } z \in [-h_0/2; h_0/2]$



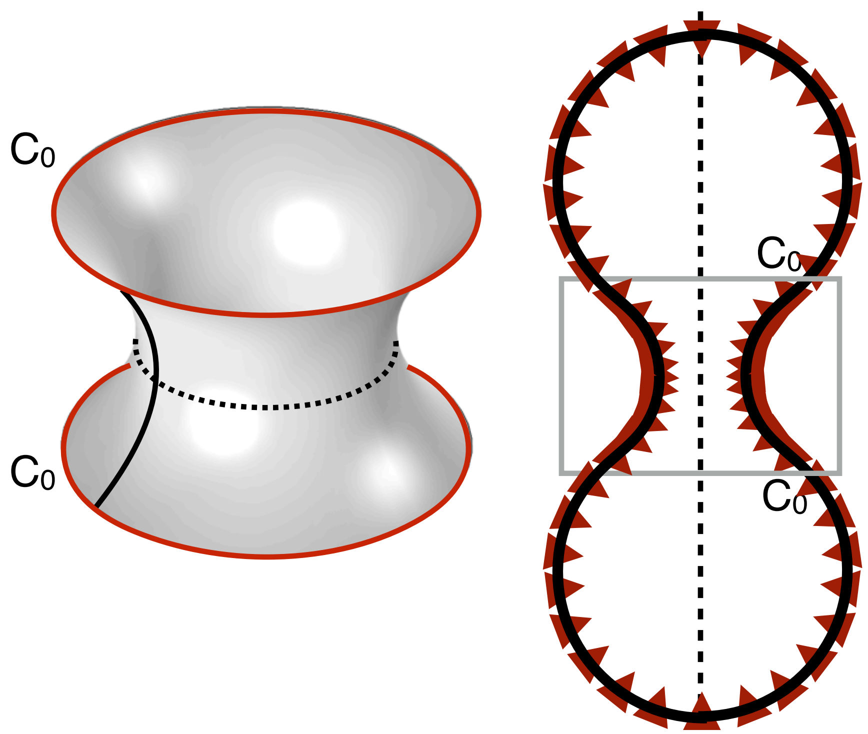
$$\Delta C(\sigma) - 2KC(\sigma) = 0$$

Gaussian curvature distribution

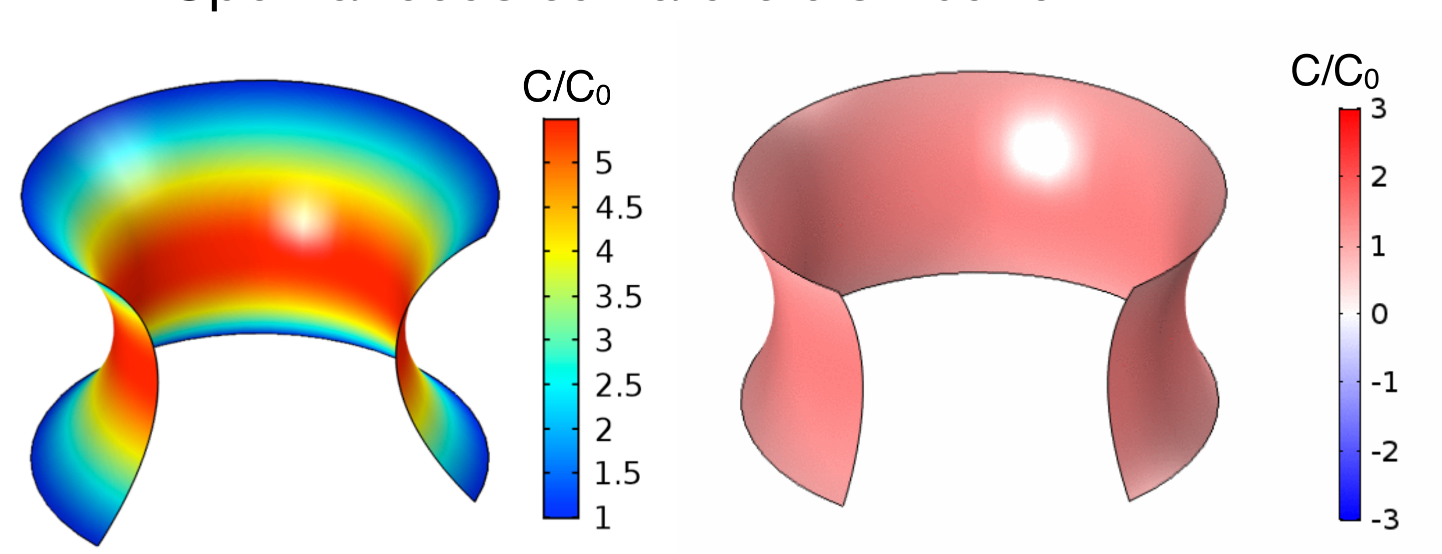
$$K = -\left[\frac{1}{r_n \cosh^2(z/r_n)}\right]^2$$
$$= -\left[\frac{1}{r_n(1+(s/r_n)^2)}\right]^2$$



- Solve for the spontaneous curvature with identical boundary conditions

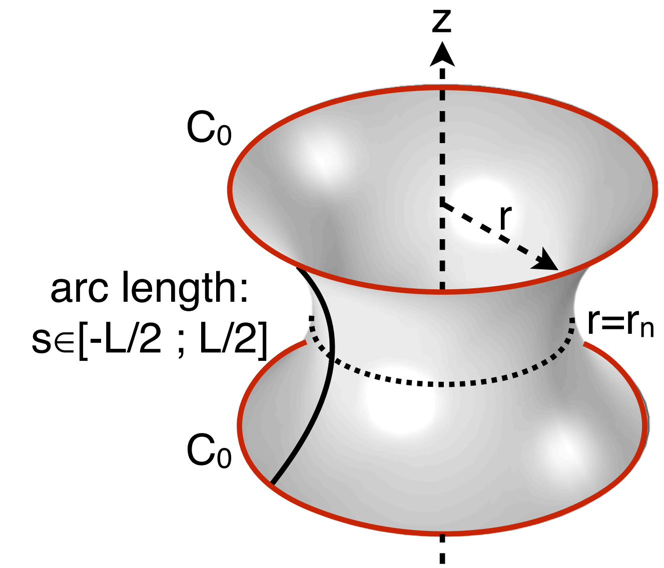


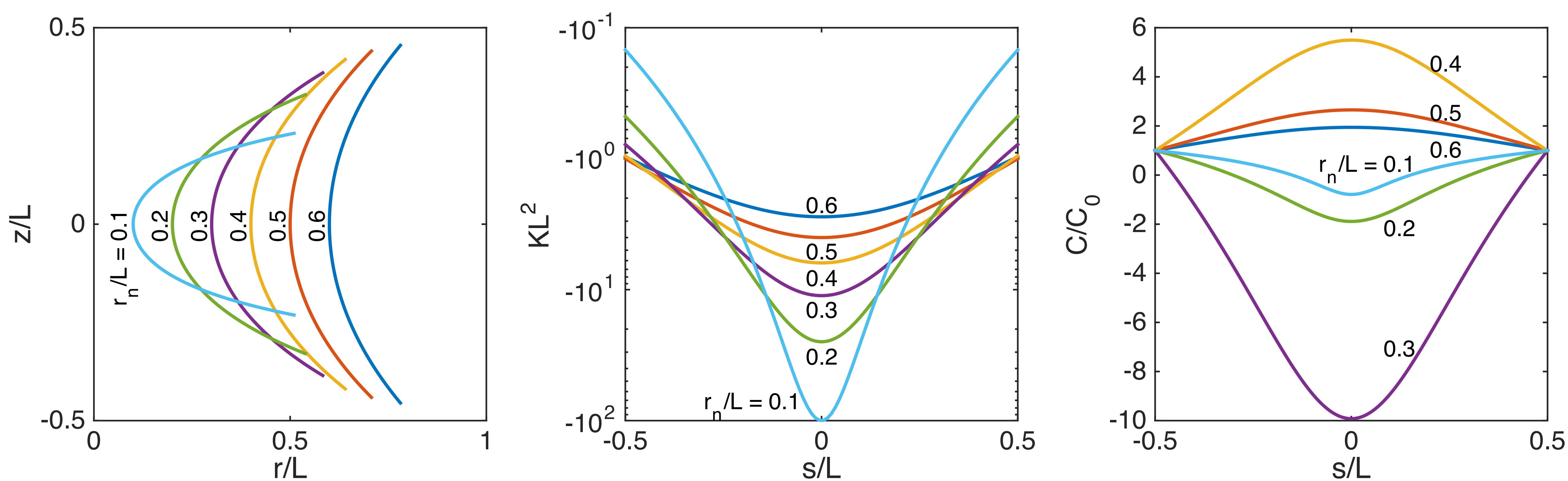
Spontaneous curvature distribution



Influence of neck radius

- **Fixed total arc length** L and identical boundary conditions C_0
- Vary **neck radius** r_n





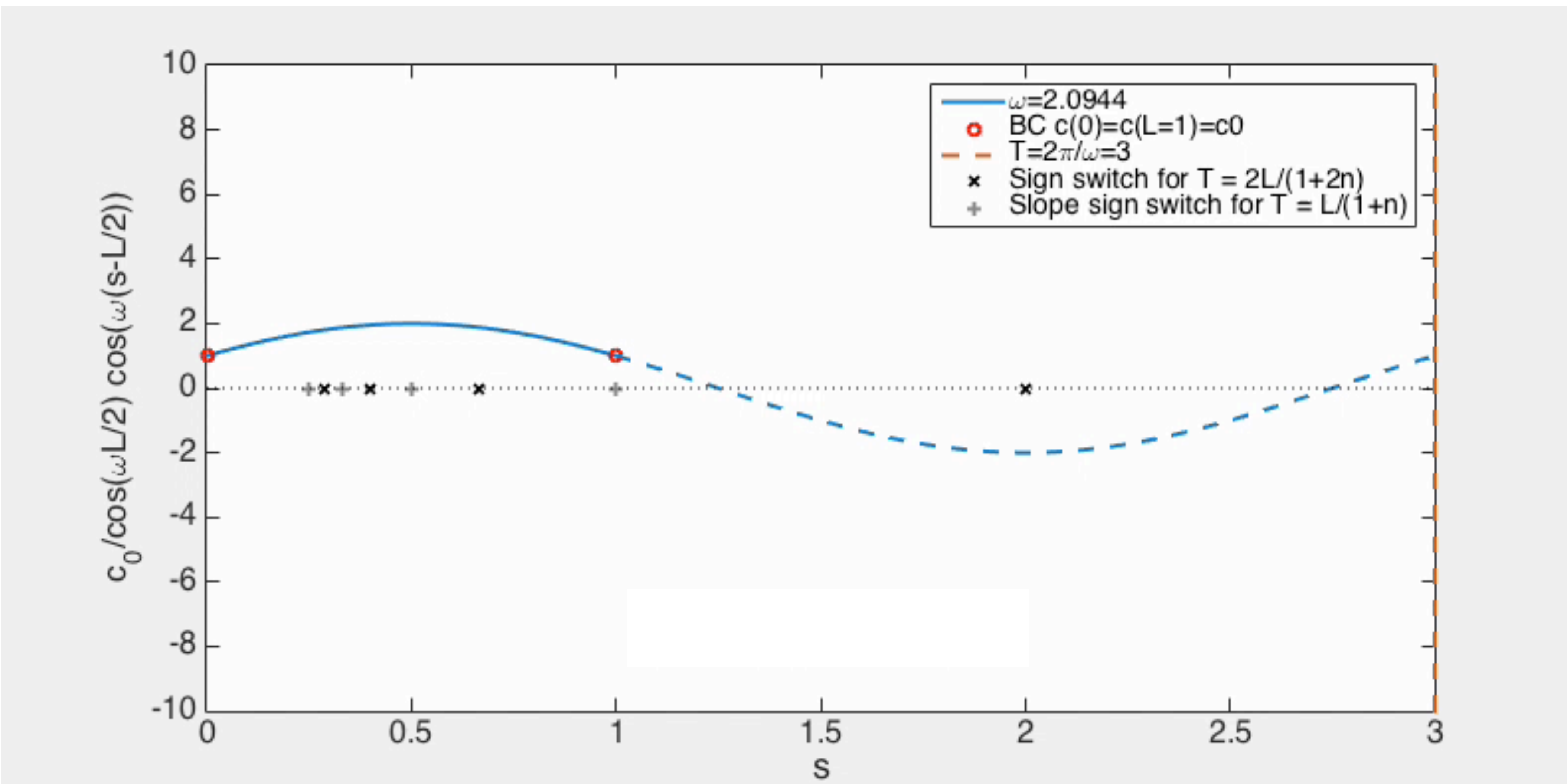
➡ **C shows a switch in sign under a critical neck radius**

Simple oscillator analogy

If K is constant $\nabla^2 C - 2KC = 0 \quad \Rightarrow \quad \dfrac{d^2 C}{ds^2} = -\omega^2 C$

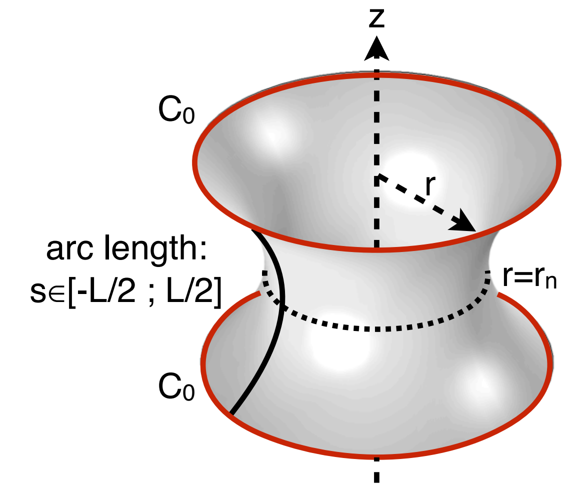
BC: $C(0) = C(L) = C_0$ $\qquad \boxed{C(s) = \dfrac{C_0}{\cos(\omega L/2)} \cos(\omega s - \omega L/2)}$

$$C(L/2) = \frac{C_0}{\cos(\omega L/2)}$$

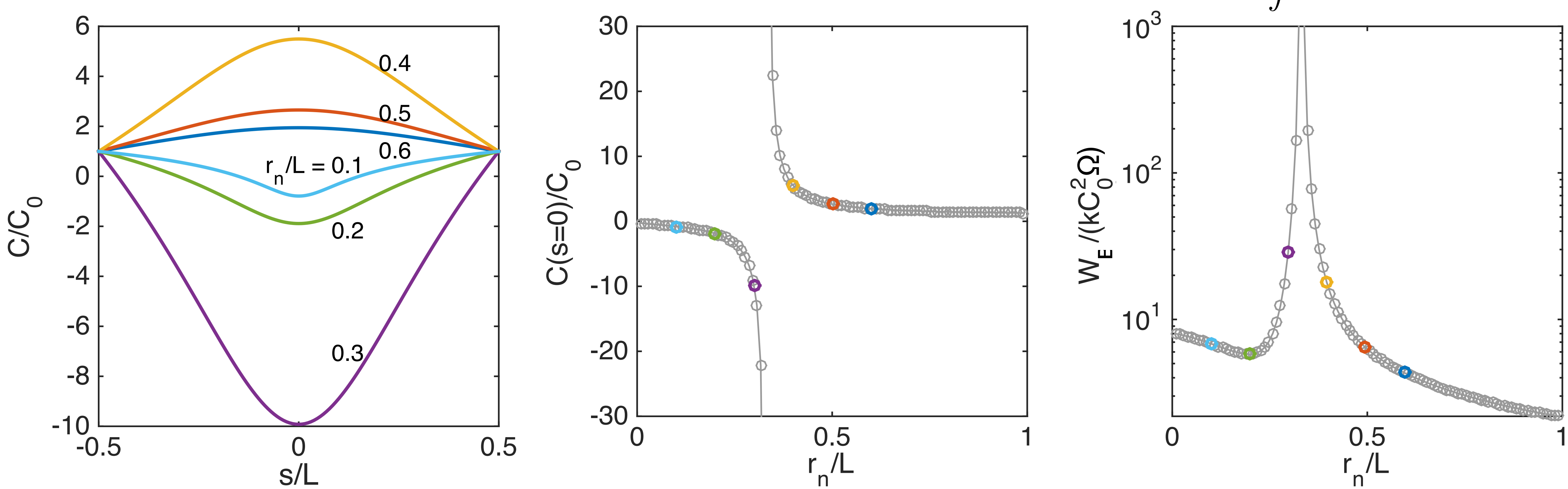


Influence of neck radius

- Existence of **energy barrier** to constrain the neck



$$W_B = \int \left(kC^2 + k_G K\right) d\omega$$

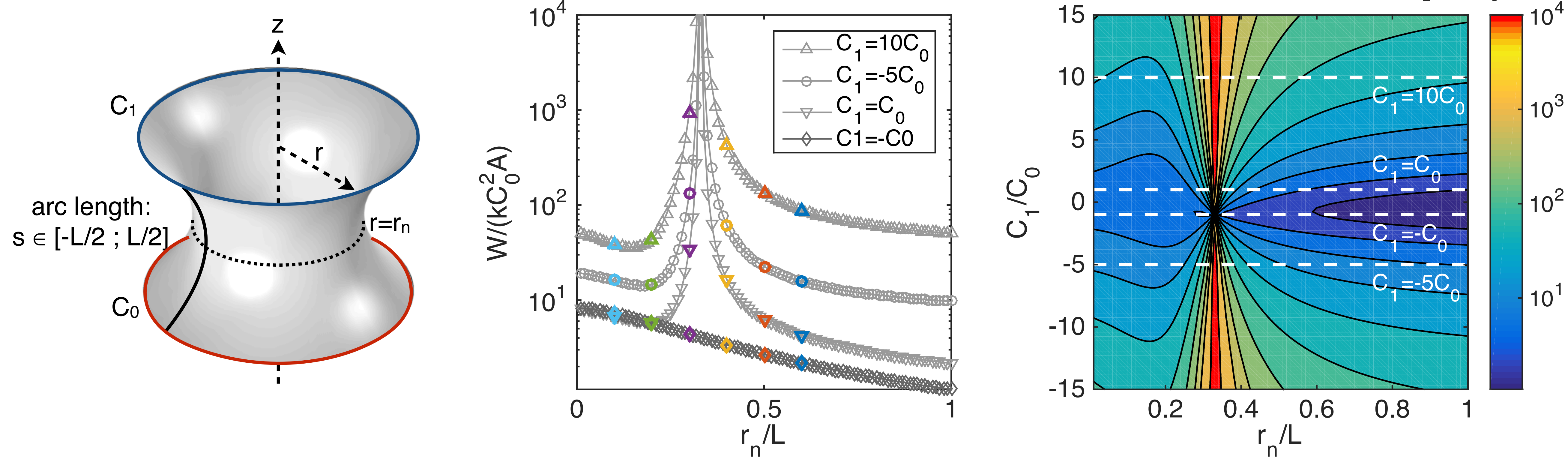


Need **at least two distinct mechanisms** to constrain a catenoid-like neck

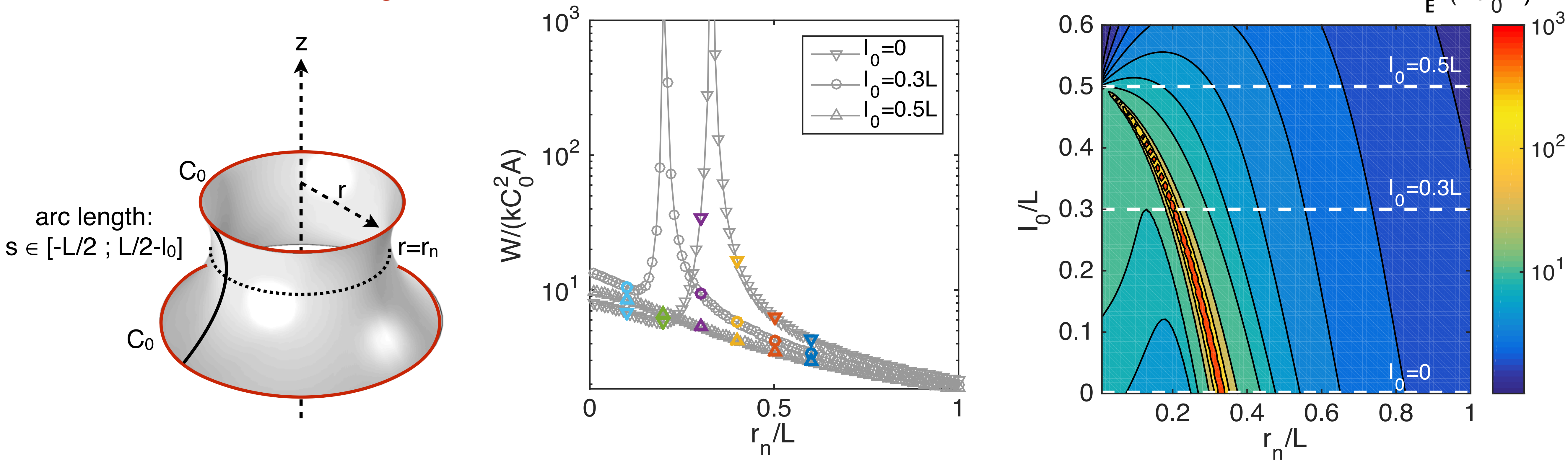
How to overcome the energy barrier to close a catenoid-like neck?

Modulation of the energy barrier

- Influence of the **boundary conditions**

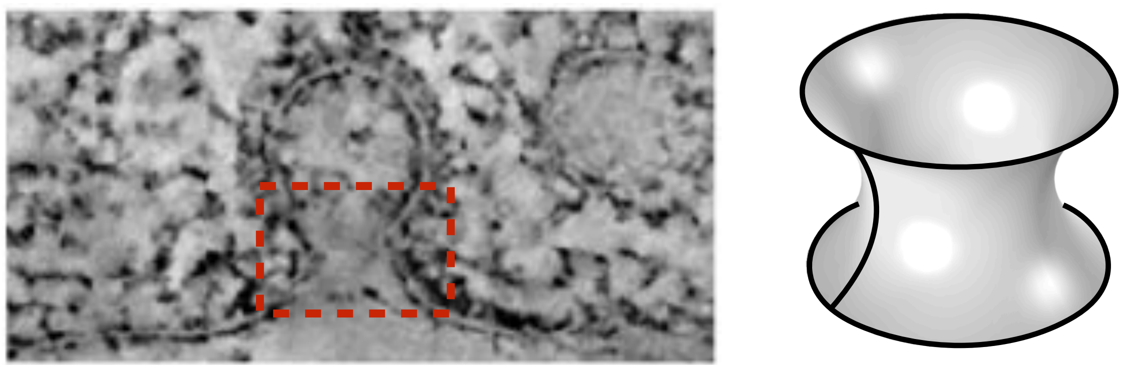


- Influence of the **geometrical asymmetry**



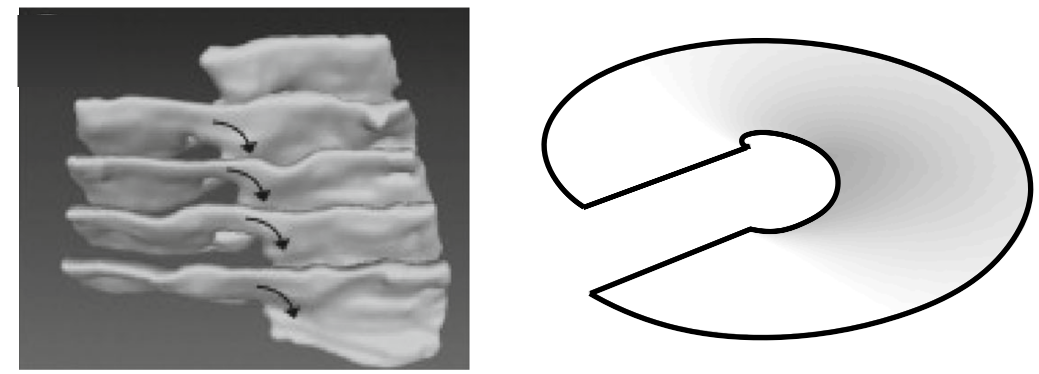
Helicoids

Catenoid-like necks



Chabanon & Rangamani, *Soft Matter* (2018)

Helicoidal ramps



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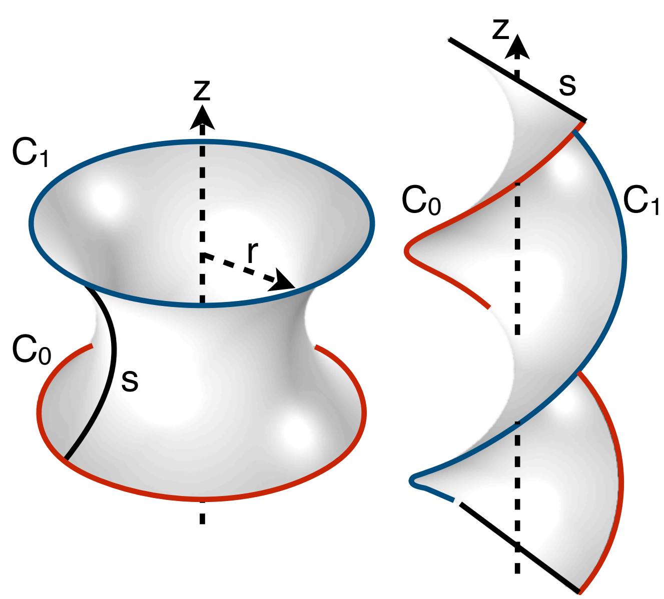
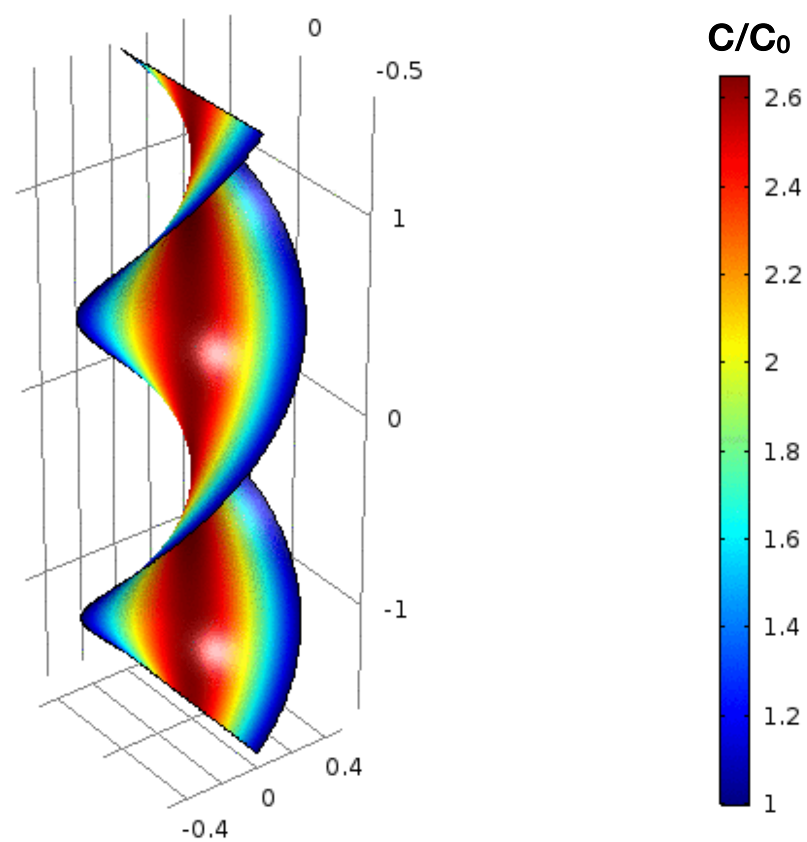
- Continuous and isometric transformation between catenoid and helicoid



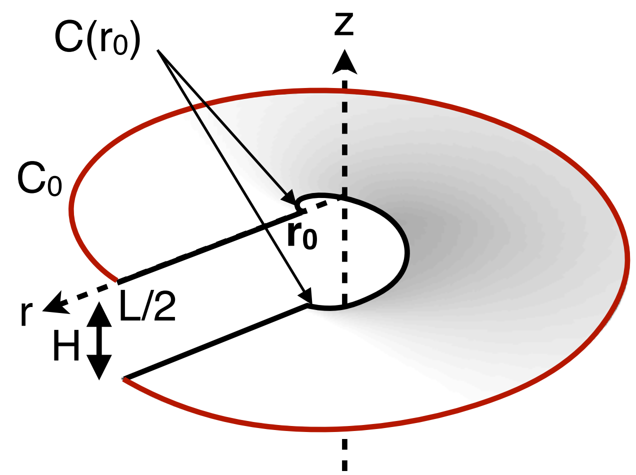


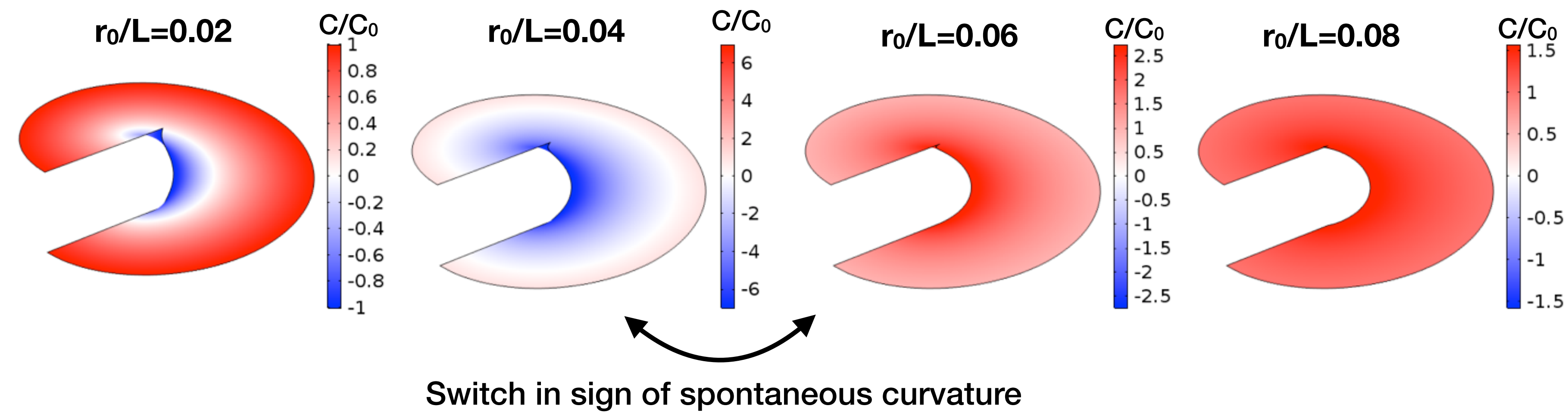
But … helicoids in the **Endoplasmic Reticulum** are more like parking ramps, with **one arm and hollow**

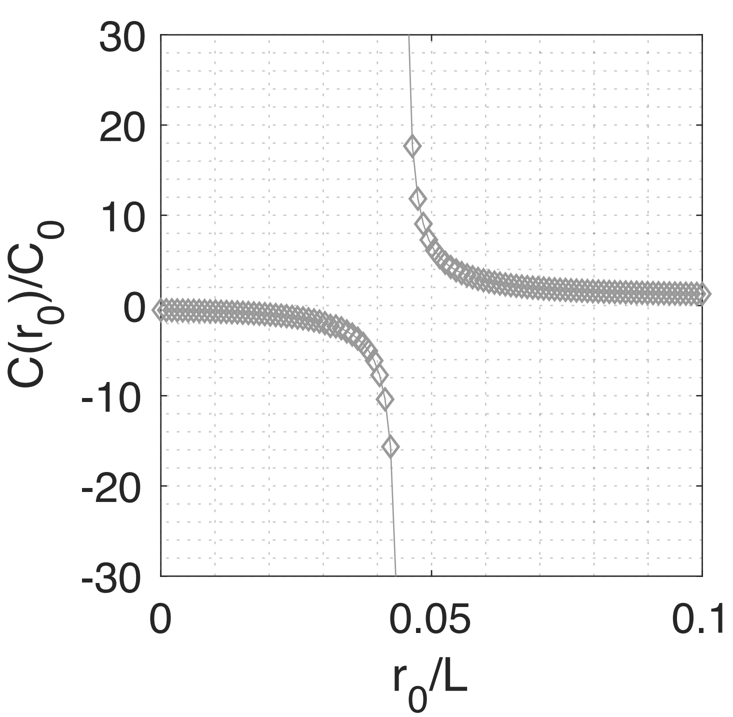
All results from catenoids hold for full helicoids

Helicoidal ramps

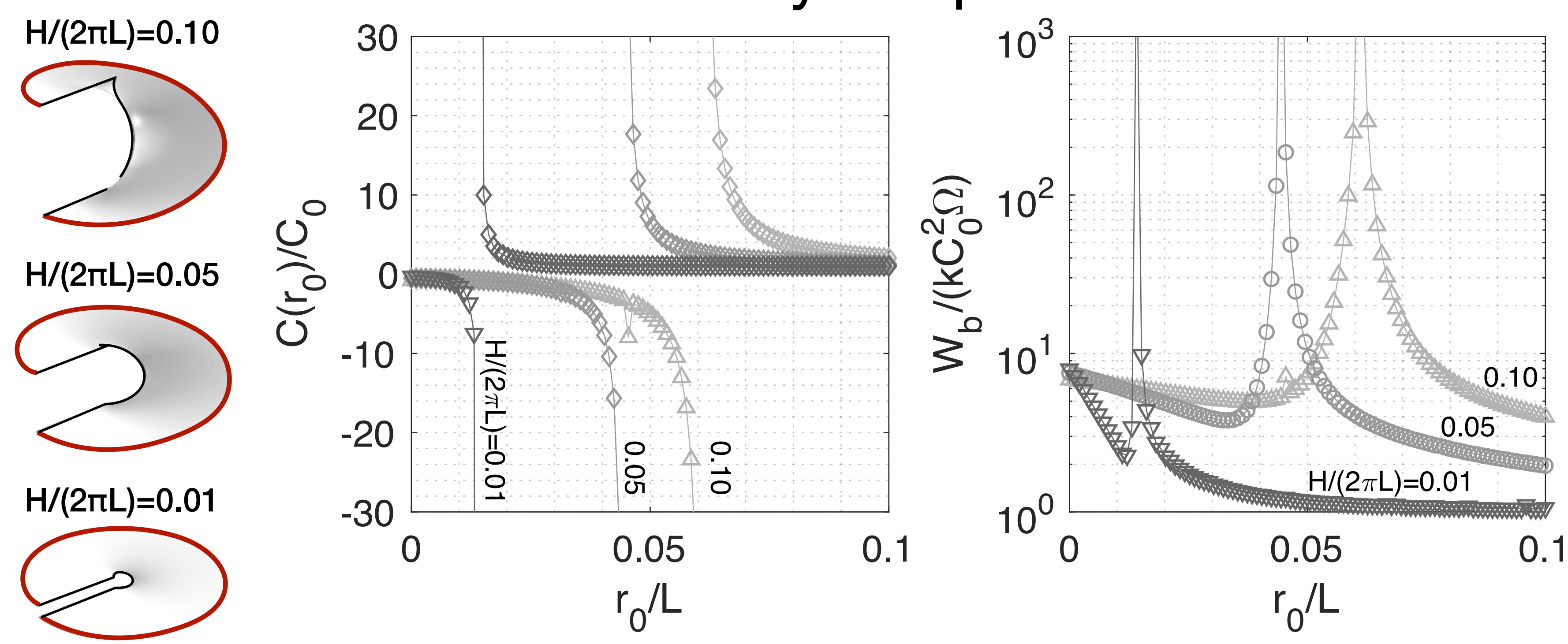
- **Switch** in spontaneous curvature with **inner radius**





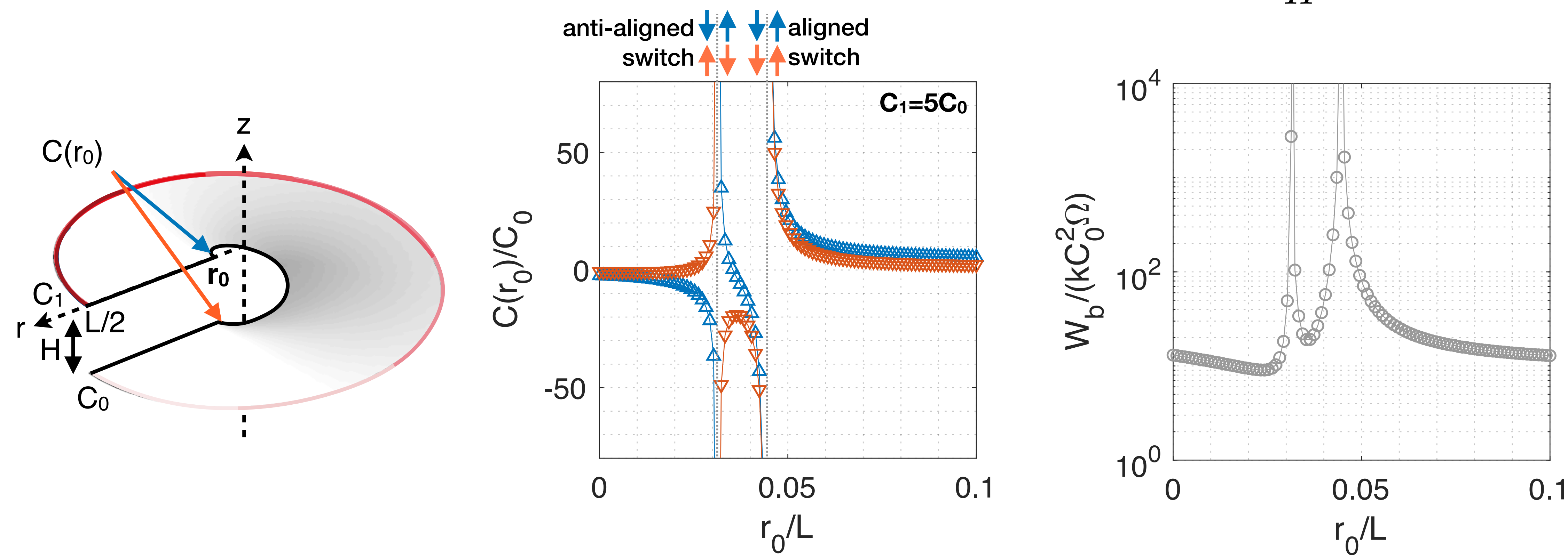


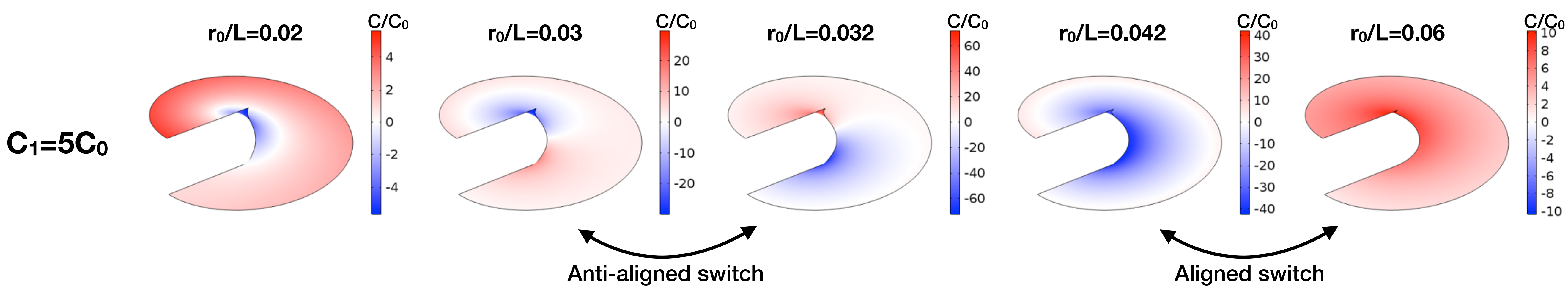
The position of the switch and energy barrier are modulated by the pitch



Helicoidal ramps with spatial variations of BC

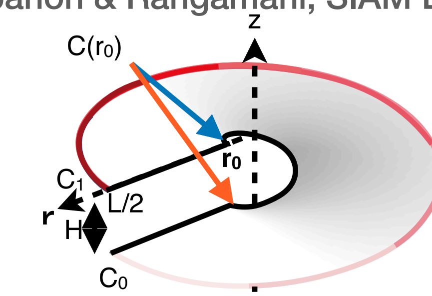
- Linear gradient at external boundary $C(z) = C_0 + (C_1 - C_0)\dfrac{z}{H}$

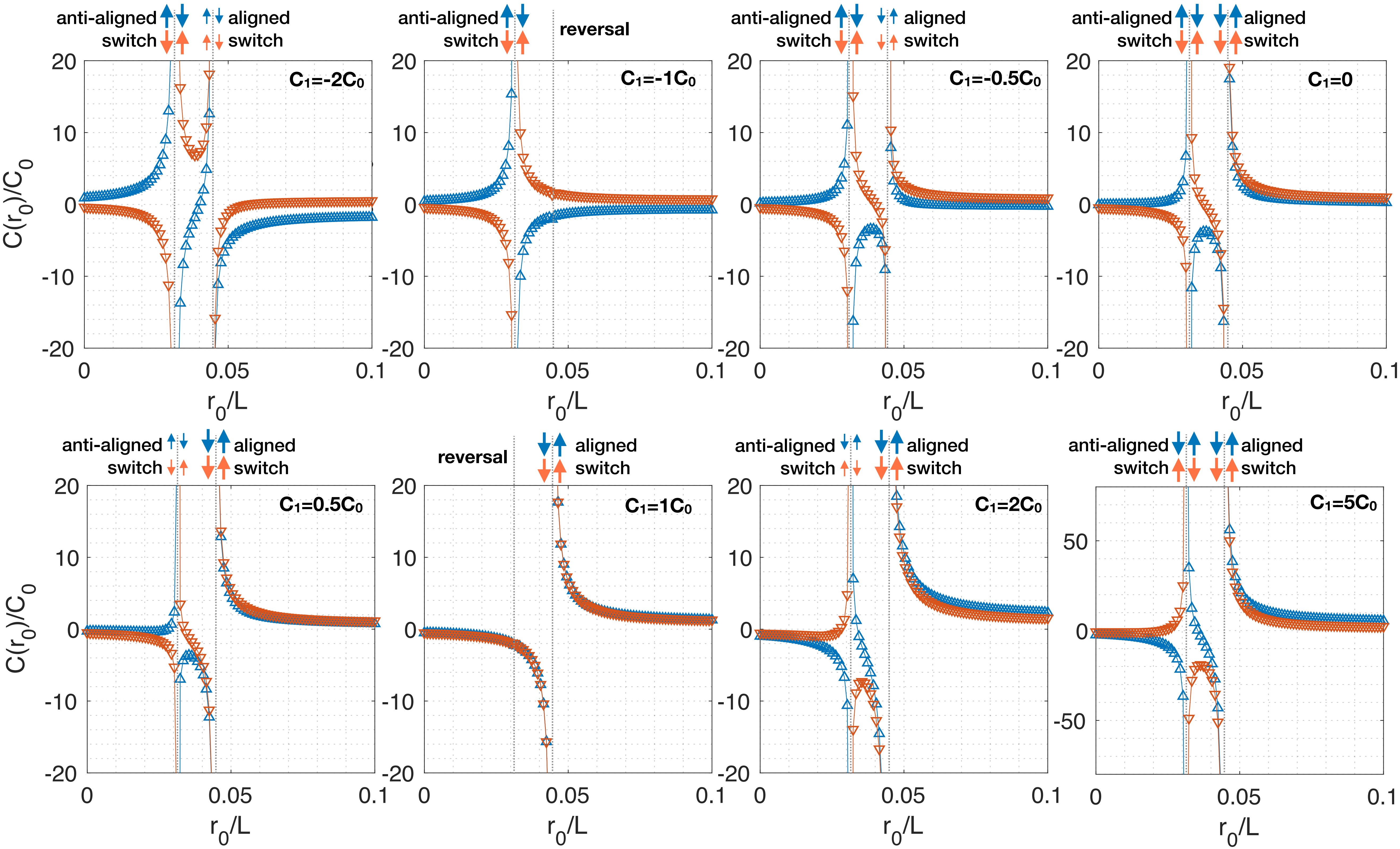




- Double energy barrier present a local minimum possibly involved in regulating ER ramps geometries

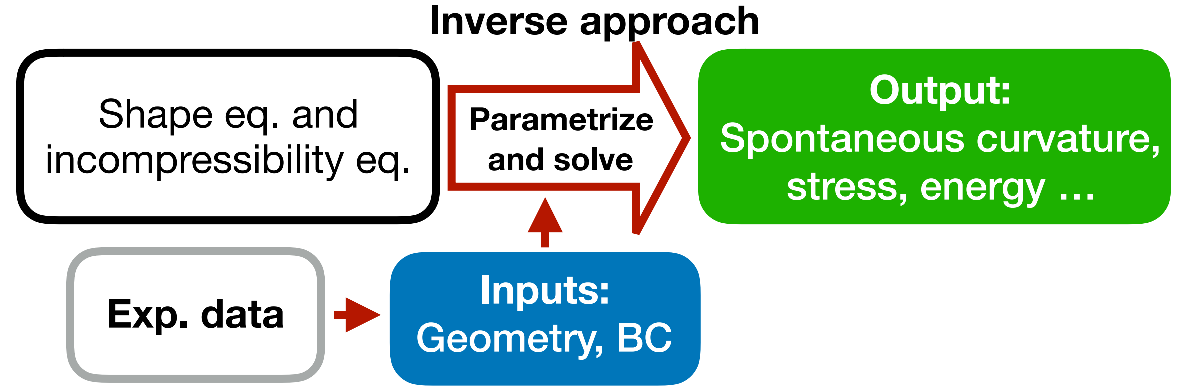
Asymmetric double switch in C



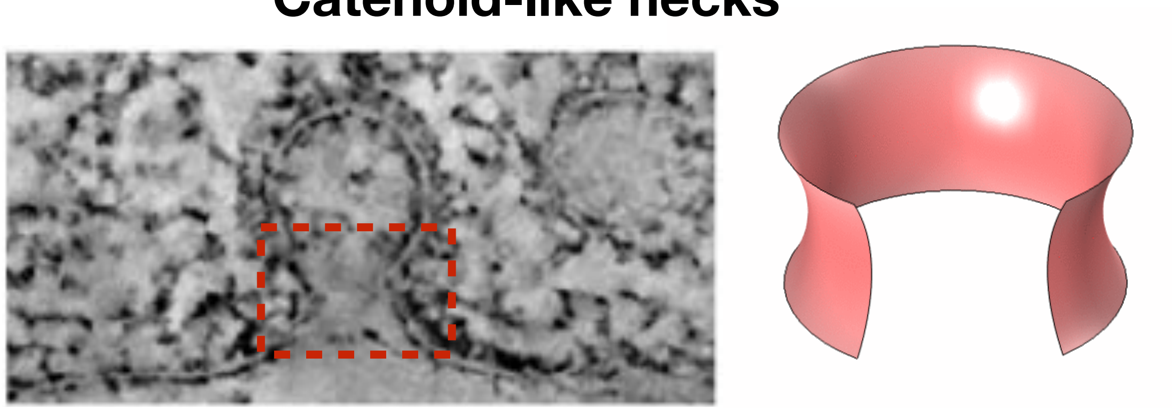


Summary

- Methodology to **compute the spontaneous curvature** required to maintaining a given **membrane structure**



Catenoid-like necks

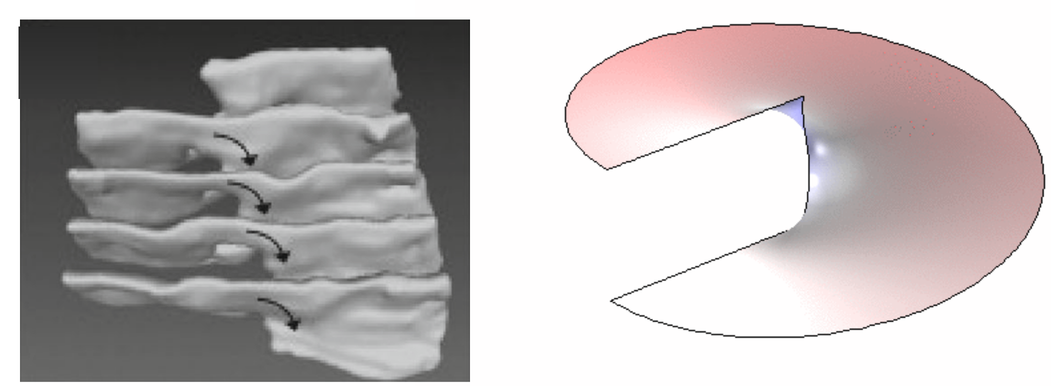


Chabanon & Rangamani, *Soft Matter* (2018)

- **Catenoid** as model for **necks**
  - Energy barrier at specific neck radius
  - Asymmetry constrain the energy landscape
- Requirement of at least 2 mechanisms to constrain **catenoid-like neck**

- **Helicoid** as model for **ER ramps**
  - Energy barrier at inner ramp radius
  - Double energy barrier for gradient of C
  - Non-trivial distribution of C
- Possible regulation mechanisms of ER ramps

Helicoidal ramps



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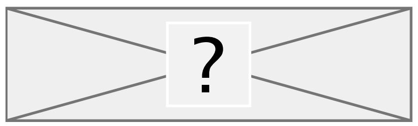
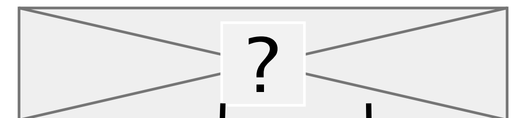
Local stress balance of elastic membranes

- **Mechanical equilibrium** of an elastic surface ω, subject to a lateral pressures p:



with the **stress vector** defined as



tangential components

$$\mathbf{T}^\alpha = T^{\alpha\beta}\mathbf{a}_\beta \quad \text{with} \quad T^{\beta\alpha} = \sigma^{\beta\alpha} + b^\beta_\mu M^{\mu\alpha}$$

normal components

$$S^\alpha = -M^{\alpha\beta}_{;\beta}$$

- Components of the **stress vector** depend on the **surface energy per area** $W(H,K;\boldsymbol{\theta}^\alpha)$

$$\sigma^{\alpha\beta} = (\lambda + W)a^{\alpha\beta} - (2HW_H + 2KW_K)\,a^{\alpha\beta} + W_H\tilde{b}^{\alpha\beta}$$

$$M^{\alpha\beta} = \frac{1}{2}W_H a^{\alpha\beta} + W_K\tilde{b}^{\alpha\beta}$$

where $\lambda(\theta^\alpha) = -[\gamma(\theta^\alpha) + W(H,K;\theta^\alpha)]$,

$$\tilde{b}^{\alpha\beta} = 2Ha^{\alpha\beta} - b^{\alpha\beta}$$

- **Normal** and **tangential** stress balance

$$\Delta\left(\frac{1}{2}W_H\right) + (W_K)_{;\alpha\beta}\tilde{b}^{\alpha\beta} + W_H(2H^2 - K) + 2H(KW_K - W) = p + 2\lambda H\,,$$

$$-(\gamma_{,\alpha} + W_K K_{,\alpha} + W_H H_{,\alpha})\,a^{\beta\alpha} = \left(\frac{\partial W}{\partial \theta^\alpha}\,|_{\exp} + \lambda_{,\alpha}\right)a^{\beta\alpha} = 0\,,$$

Steigmann, *Arch Ration Mech Analysis* (1999). Rangamani et al., *Biomech Model Mechanobiol* (2013), *Biophys J* (2014)