Mathematical modeling of the motility of euglena cells

shape transformations, force generation, and the interaction with the environment

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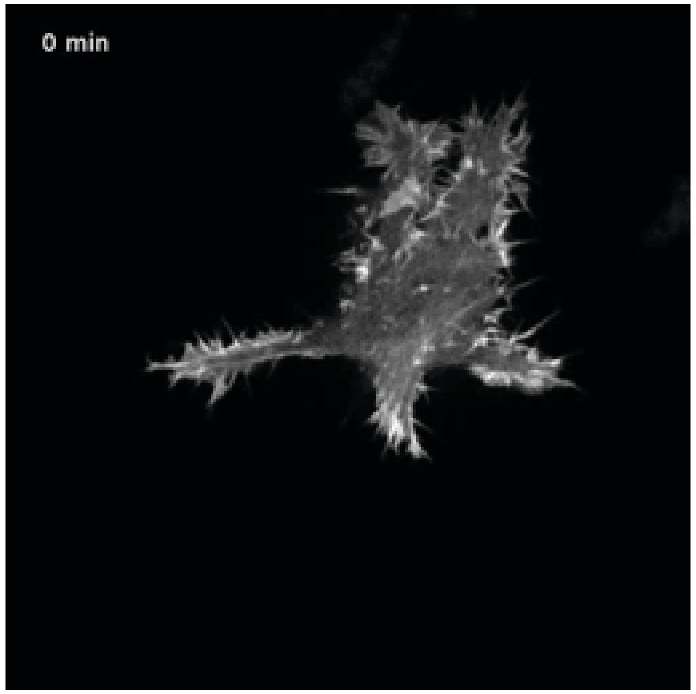
BGSMath, June 2016

UNIVERSITAT POLITÈCNICA DE CATALUNYA

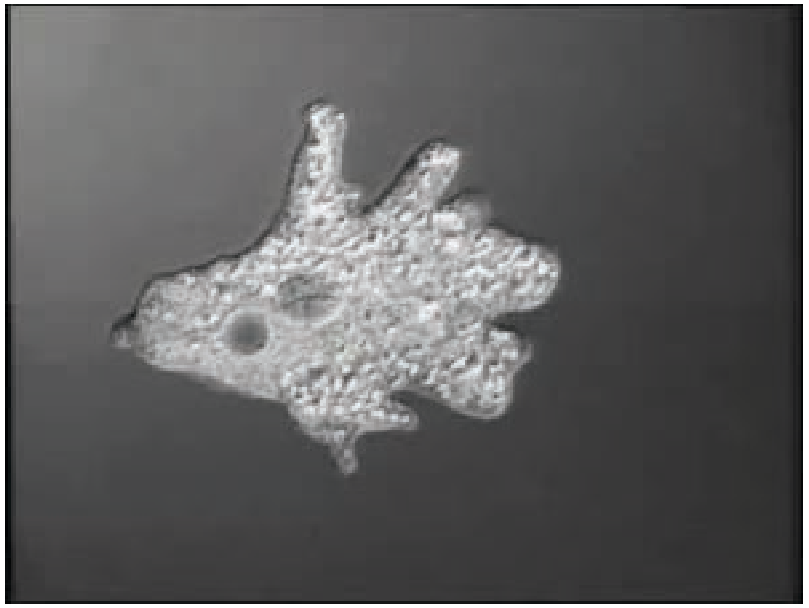
LaCàN

Cell motility: locomotion at the micron scale

fibrous 3D matrix **2D solid substrate** **fluid**

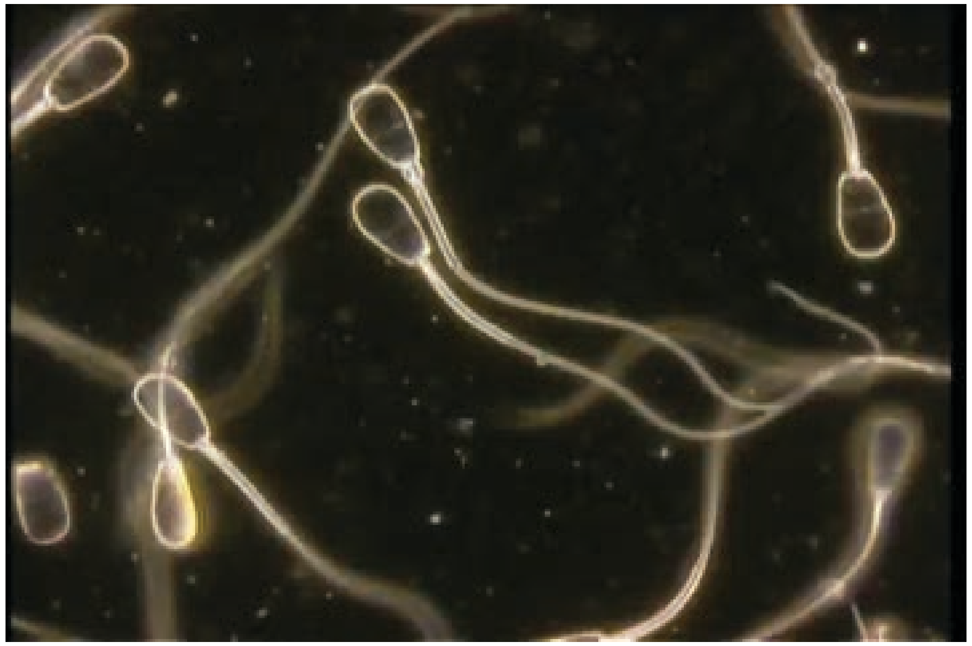


Cancer cell
(Humphries Lab)



Amoeboid movement

collective migration of epithelial cells



Sperm cells

cell size ~10s microns

Swimming at the micron scale

Hydrodynamic equations are not scale-invariant:

$$\rho\left(\frac{\partial v}{\partial t}+(\nabla v)v\right)=\eta\Delta v-\nabla p$$
$$\mathrm{div}\ v=0$$

Navier-Stokes (nonlinear)

Non-dimensionalize: $x_*=\dfrac{x}{L},\quad t_*=\dfrac{t}{T},\quad p_*=\dfrac{p}{\eta V},\quad v_*=\dfrac{v}{V}$

$$\sigma\,\mathrm{Re}\,\frac{\partial v_*}{\partial t_*}+\mathrm{Re}\,(\nabla_* v_*)v_*=\Delta v_*-\nabla_* p_*$$
$$\mathrm{div}_*\ v_*=0$$

$$\mathrm{Re}=\frac{\mathrm{V\,L}\,\rho}{\eta}\qquad \sigma=\frac{\mathrm{L}}{\mathrm{VT}}$$

$$0=\eta\,\Delta v-\nabla p$$
$$\mathrm{div}\ v=0$$

Stokes
formal limit Re→0
(linear)

Swimming at the micron scale

Reynolds number:

$$\mathrm{Re} = \frac{\mathrm{V\,L}\,\rho}{\eta}$$

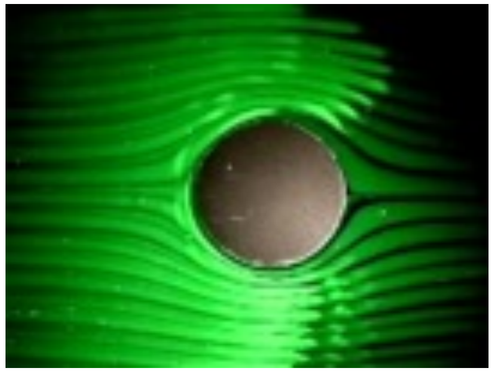
Velocity (typical order of magnitude)	V
Diameter (typical length scale)	L
Mass density of the fluid	ρ
Viscosity of the fluid	η

Re is a dimensionless measure of relative importance of inertia vs. viscosity

For water at room temperature: $\rho/\eta = 10^6(\mathrm{m}^2\mathrm{s}^{-1})^{-1}$

Orders of magnitude for swimmers:

Men, sharks:	L=1m, V=1-10 ms^{-1}	Re= 10^6-10^7
Bacteria:	L=1x10^{-6}m, V=1-10x10^{-6} ms^{-1}	Re=10^{-6}–10^{-5}



At micron scale neglect all inertial forces (for both fluid and swimmer)

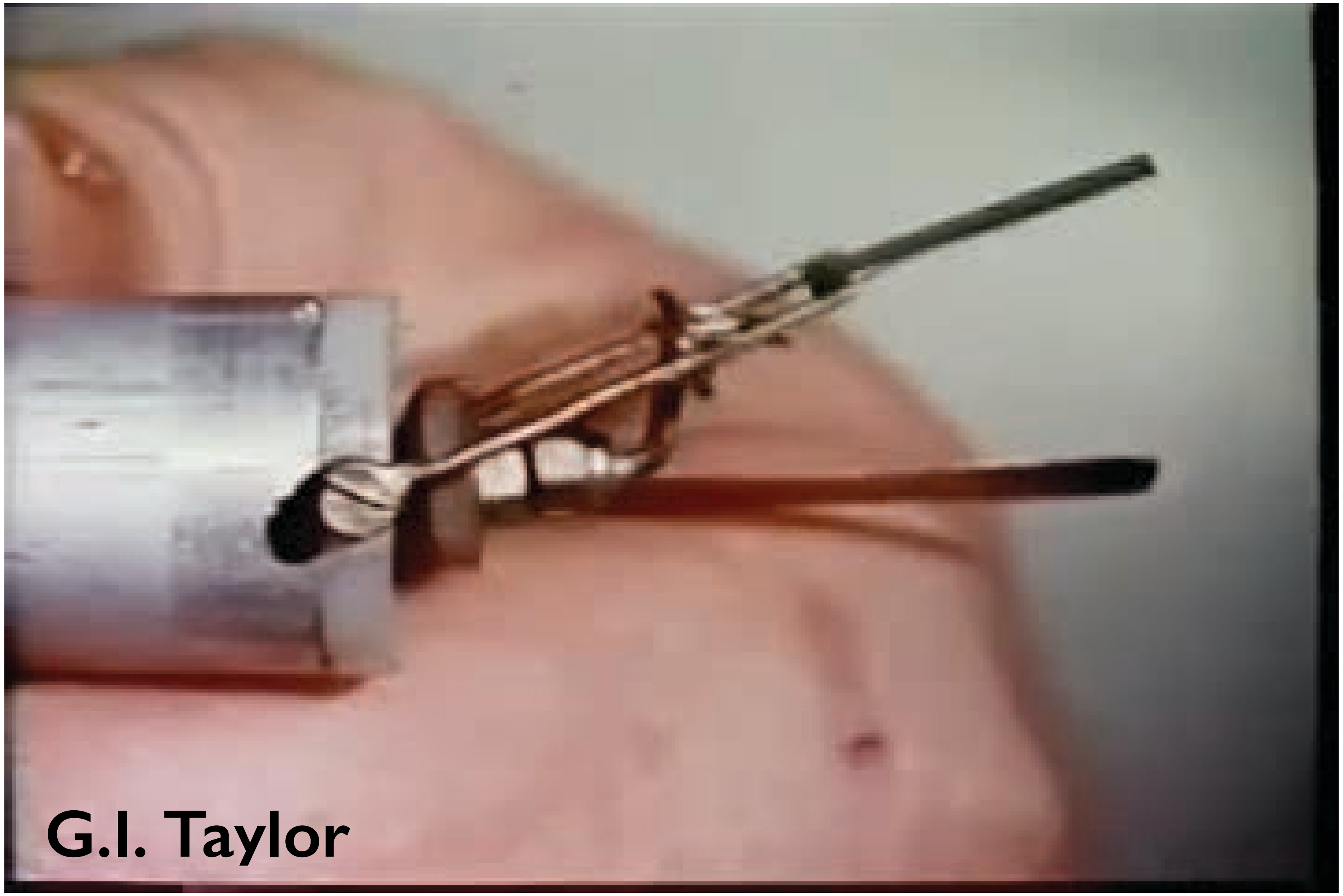
Swimming at the micron scale

Is swimming without inertia much different?

$$0 = \eta\,\Delta v - \nabla p$$

$$\text{div}\ v = 0$$

$$\text{Re} = \frac{\text{V}\,\text{L}\,\rho}{\eta}$$

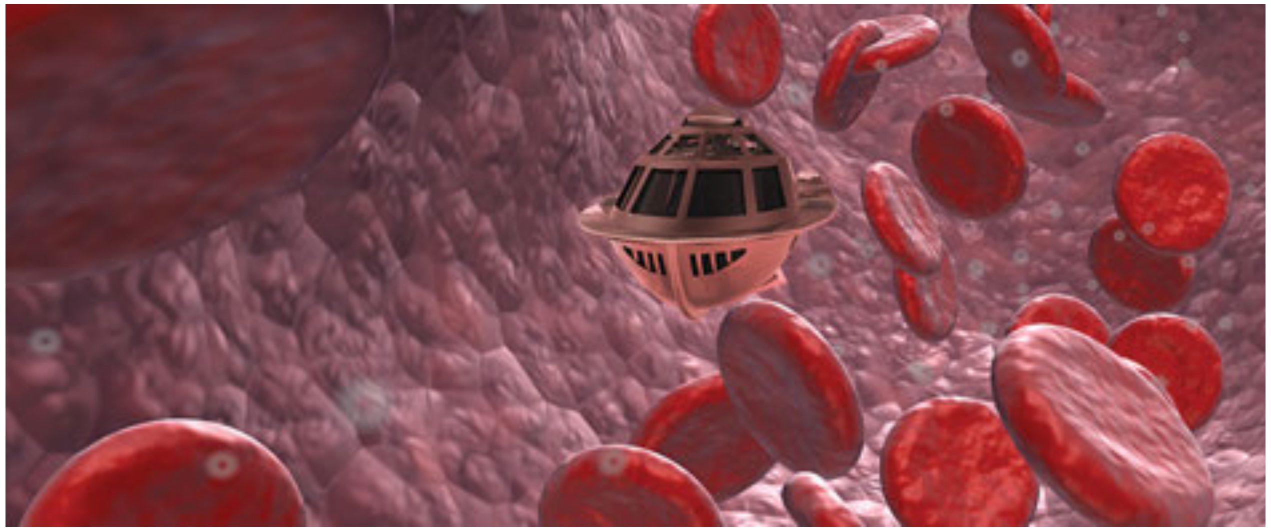


Purcell's *scallop theorem:* trying to swim by a reciprocal stroke at low Re is condemned to frustration.

Swimming at the micron scale

Swimming at low Re abides by very different, counter-intuitive rules, and requires a miniaturized motile machinery.

- how do micro-organisms swim? what biological structures are required?
- do they swim optimally? in what sense and driven by which evolutionary pressure?
- can we engineer microscopic self-propelled devices, e.g. for drug delivery, for diagnostic or therapeutic purposes?



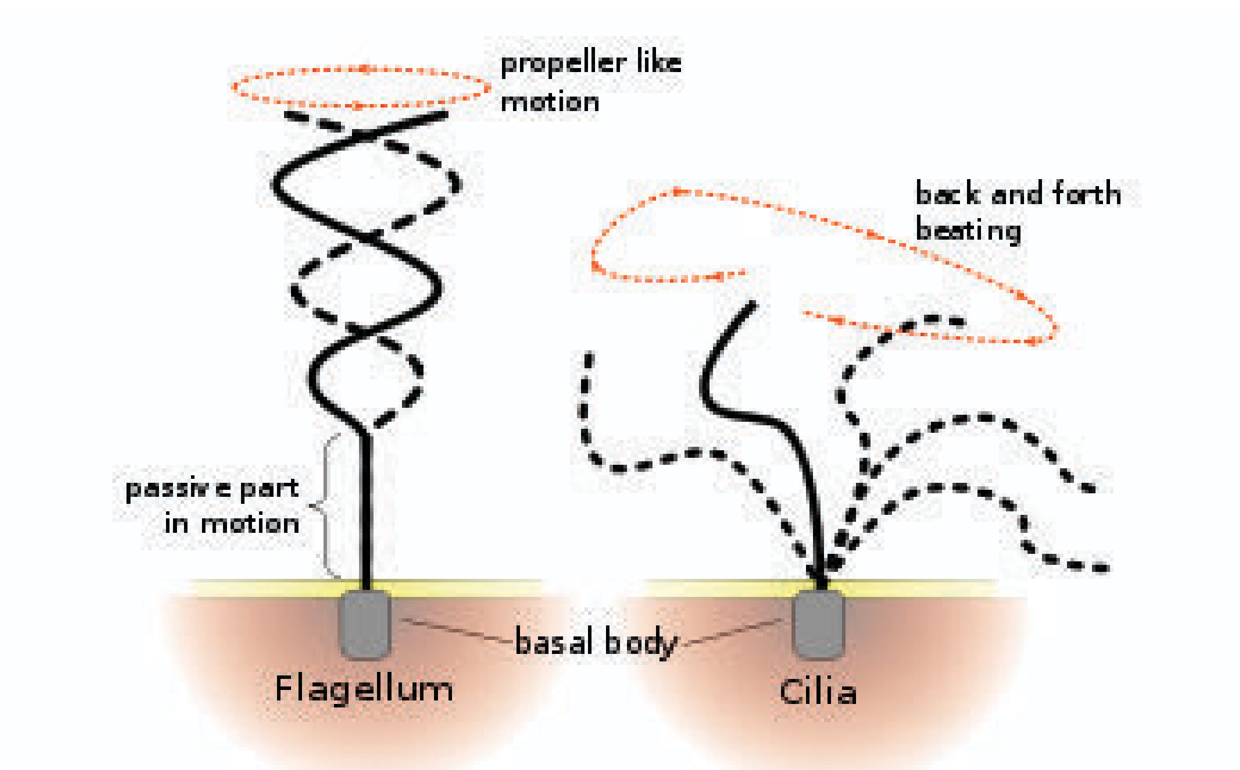
Fantastic voyage (1966)

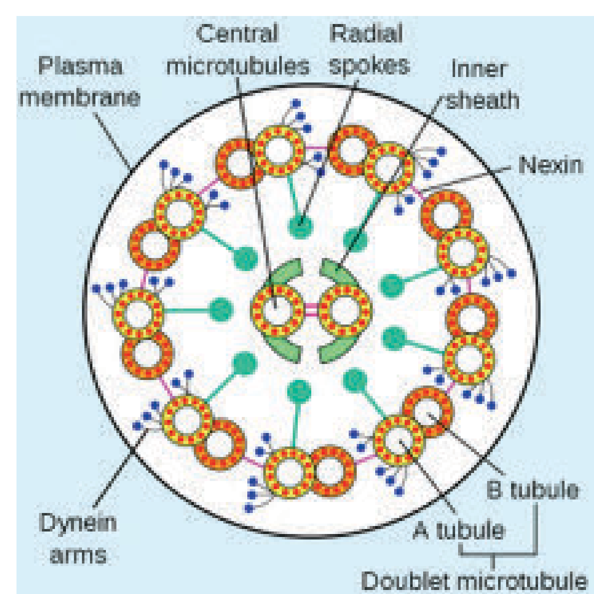
RBC + magnetic flexible filament

Dreyfus et al, Nature'05

Swimming at the micron scale

Most unicellular micro-organisms swim by beating cilia or flagella.

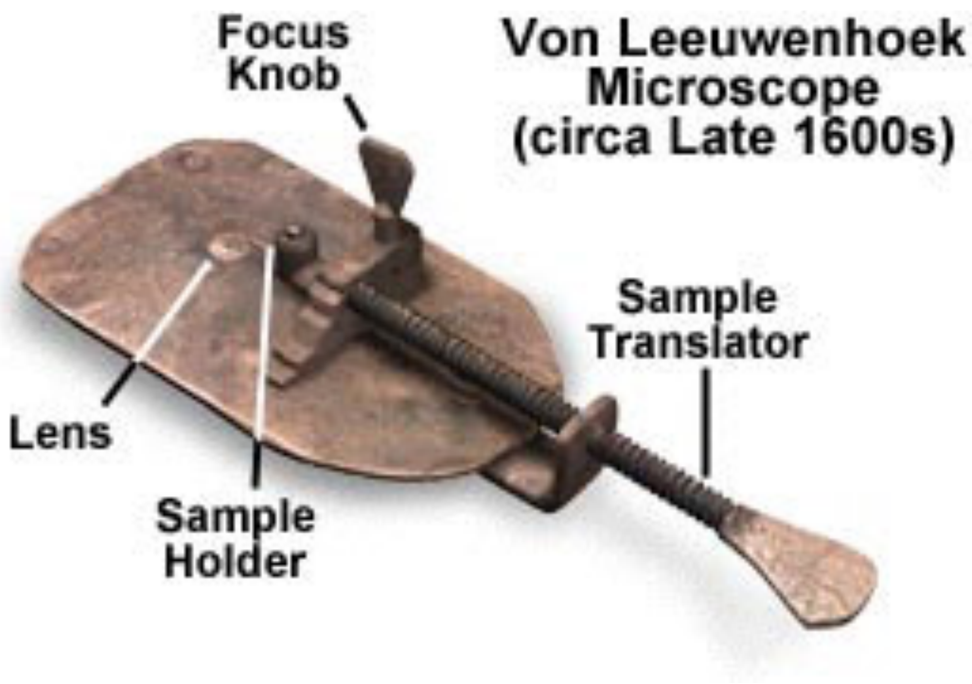


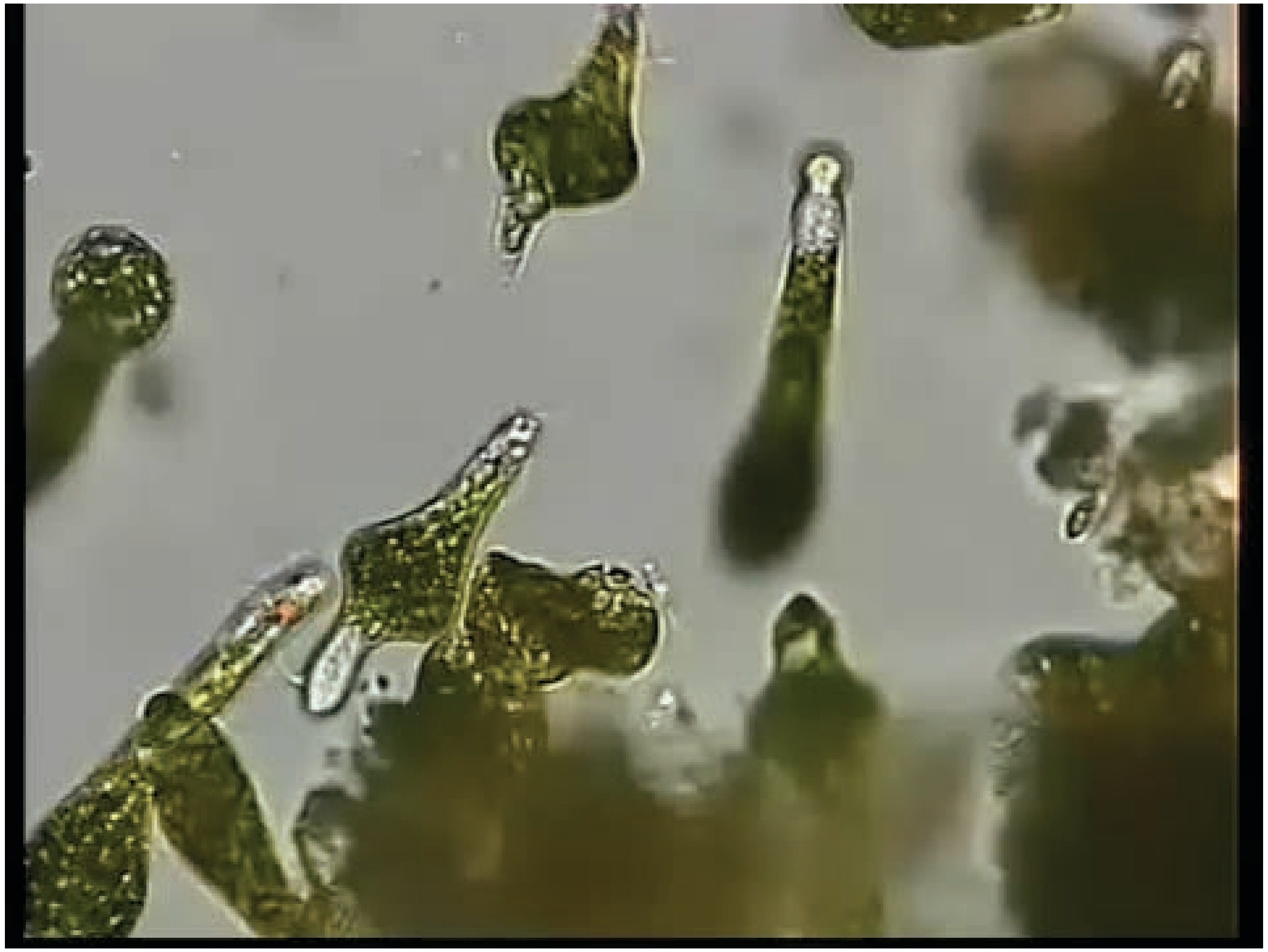


system of microtubules and molecular motors

euglenoid movement or *metaboly*

euglenoid movement or *metaboly*





van Leeuwenhoek described in 1674 **microscopic motile "animalcules" that were green in the middle…**

… which challenged classification of organisms as either animals or plants.

a beautiful mystery

Metaboly coexists within individuals with flagellar locomotion, perceived as the main motility mode.

Its evolutionary origin and actuation mechanism is unclear, and its function controversial.

Fletcher&Theriot'04

Table 1. Cell movements and their molecular mechanisms.

Cell movement	Cell structure needed	Molecular motor	Motor category
Movements through liquid			
Bacterial swimming	Flagella (bacterial)	Flagellar rotor (MotA/MotB)	Rotary
Eukaryotic swimming	Cilia, flagella (eukaryotic)	Dynein	Linear stepper
$\boxed{\text{Metaboly}}$	Unknown	Unknown	Unknown
Movements on solid surfaces			
Amoeboid motility (crawling)	Lamellipodia, filopodia, pseudopodia	Actin	Assembly/disassembly
		Myosin (several)	Linear stepper
Bacterial gliding	Junctional pore complex	Slime extrusion nozzle	Extrusion

goals

Using simple observations, mathematical models and biophysical arguments:

- what is the purpose of metaboly? is it a competent mode of locomotion? why bother if you also have flagella?
- how are these elegant shape reconfigurations performed?
- can we draw inspiration from euglena for new technologies?

outline

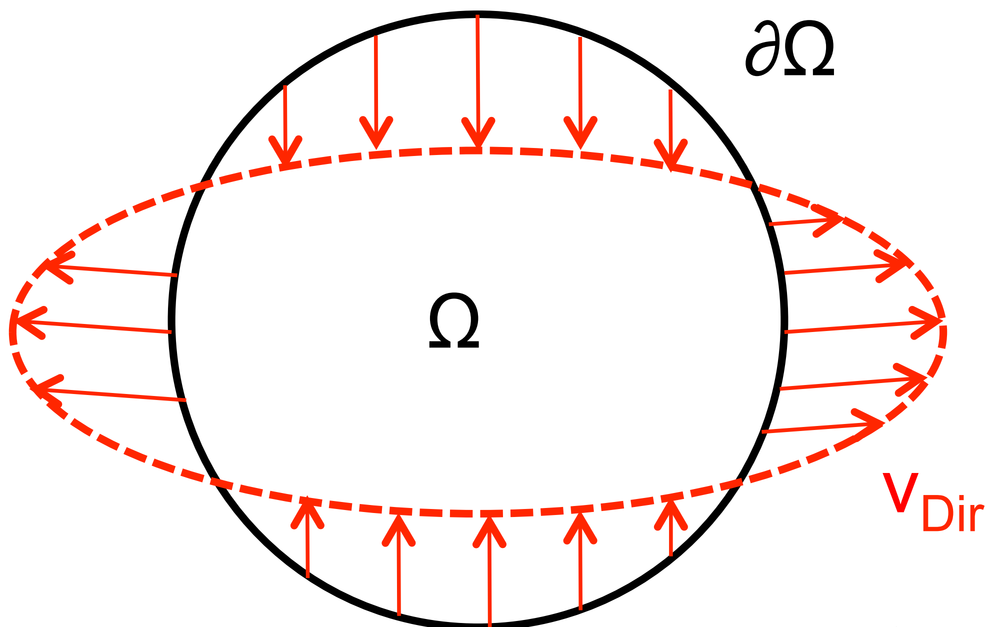
1. micro-swimming with a few formulae
2. qualitatively examining swimming euglena
3. a detour: the actuation mechanism
4. back to the motility of euglena

micro-swimming with a few formulae

Swimming: ability to advance in a fluid in the absence of external propulsive forces by performing cyclic shape changes.

micro-swimming with a few formulae

1. Find u,p in the surrounding fluid induced by swimmer's shape changes:



$$\begin{cases} -\eta\Delta u + \nabla p = 0 \\ \mathrm{div}\, u = 0 \end{cases} \quad \text{on } \mathbb{R}^3 \setminus \Omega$$

u = v_{Dir} on ∂Ω

$$u \to 0 \quad \text{at infinity.}$$

$$F_{visc} = \int_{\partial\Omega} \sigma_{visc}\, n\, dA = \int_{\partial\Omega} DN_{\Omega}[v_{Dir}]\, dA$$

Not all of v_{Dir} is a-priori known (only shape is given, not position)

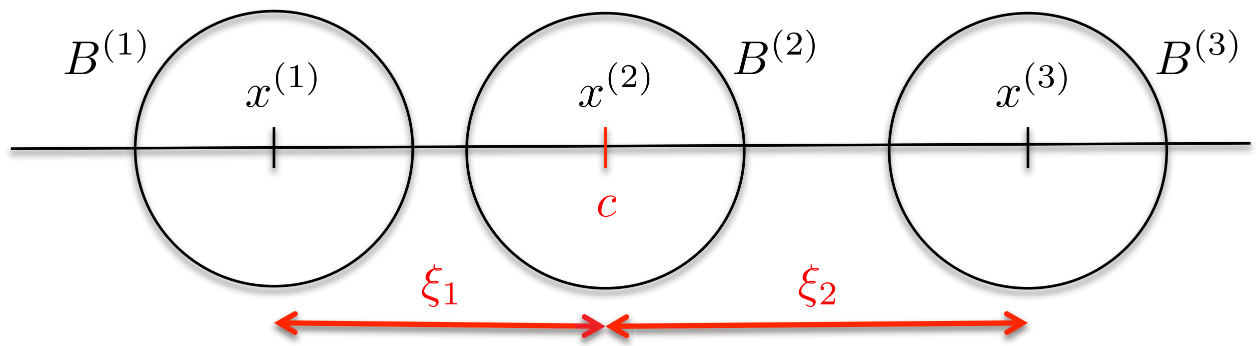
2. Find swimmer's translational and rotational velocities by solving

Total (viscous) force = 0 Total (viscous) torque = 0

$$F_{visc}[v_{Dir}] = F_{visc}[\,\dot{c}, \dot{\xi}\,] = 0\,; \quad c = position + orientation\,, \xi = shape\,.$$

a minimal axisymmetric swimmer

$$F_{visc}[\,\dot{c}, \dot{\xi}\,] = 0\,; \quad c = position\,,\, \xi = shape\,.$$



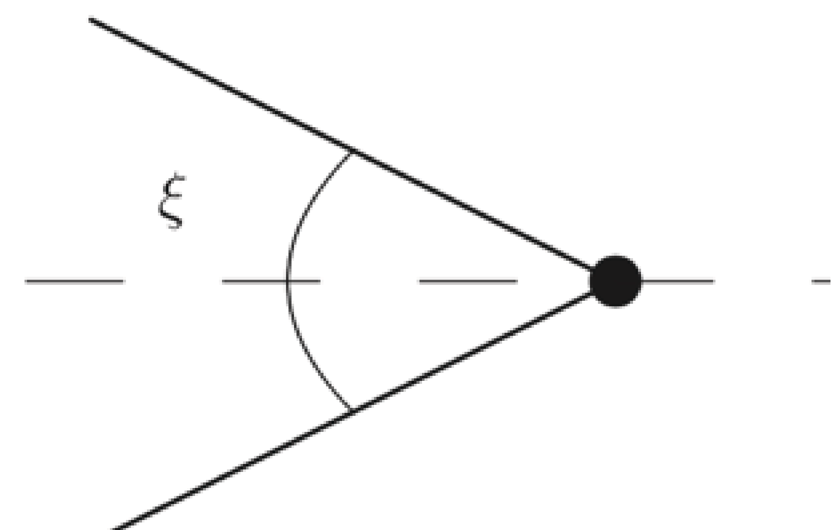
Linearity of Stoke's equations

$$0 = \varphi_1(\xi, c)\dot{\xi}_1 + \varphi_2(\xi, c)\dot{\xi}_2 + \varphi_3(\xi, c)\dot{c} \qquad \varphi_i(\xi, c) = \varphi_i(\xi)\,, \quad \varphi_3 > 0$$

$$\dot{c} = V_1(\xi)\,\dot{\xi}_1 + V_2(\xi)\,\dot{\xi}_2 \qquad V_i(\xi) := -\frac{\varphi_i(\xi)}{\varphi_3(\xi)}, \quad i = 1, 2$$

Motility map for 1 dof swimmer

$$\Delta c = \int_0^T \dot{c}\; dt = \int_0^T V(\xi(t))\dot{\xi}(t)\; dt$$
$$= \int_0^T \frac{d}{dt}\psi(\xi(t))\; dt = \psi(\xi(T)) - \psi(\xi(0)) = 0.$$

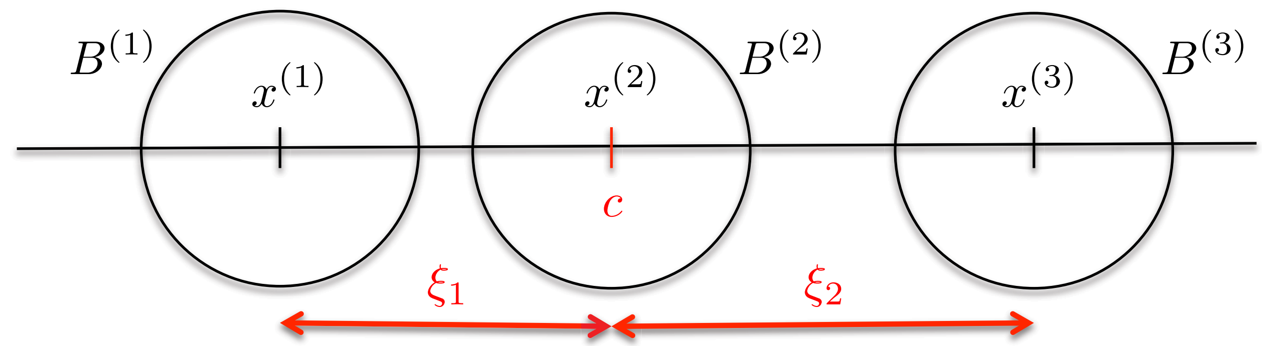


Purcell's *scallop theorem*

F. Alouges, A. DeSimone, JNLS'08

a minimal axisymmetric swimmer

$$F_{visc}[\dot{c}, \dot{\xi}] = 0\,; \quad c = position\,, \xi = shape\,.$$



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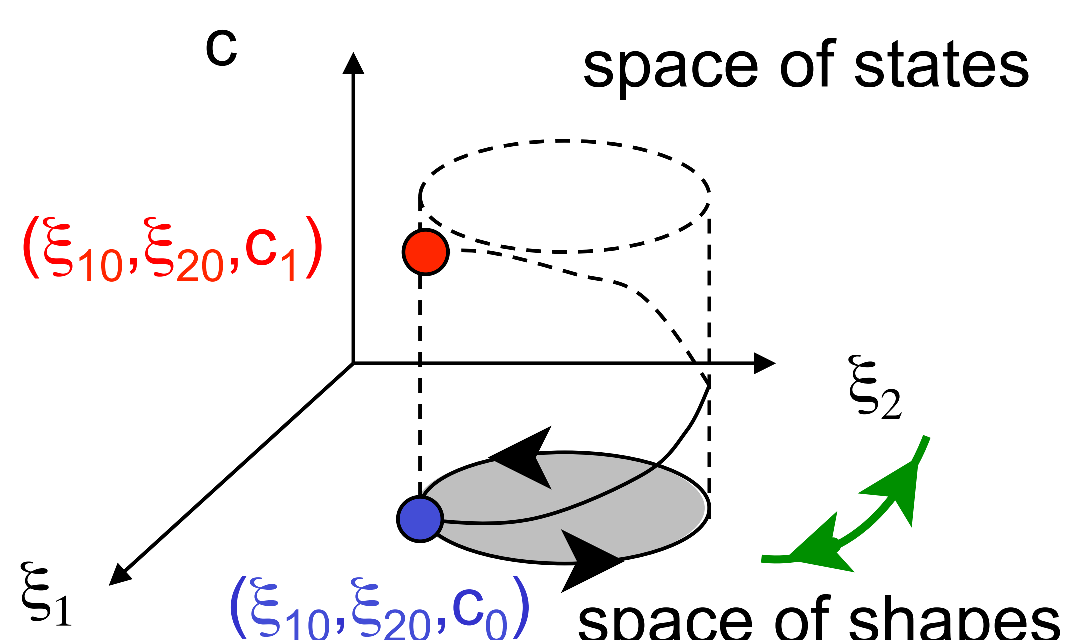
$$\dot{c} = V_1(\xi)\,\dot{\xi}_1 + V_2(\xi)\,\dot{\xi}_2 \qquad V_i(\xi) := -\frac{\varphi_i(\xi)}{\varphi_3(\xi)}, \quad i = 1, 2$$

Motility map for 2 dof swimmer

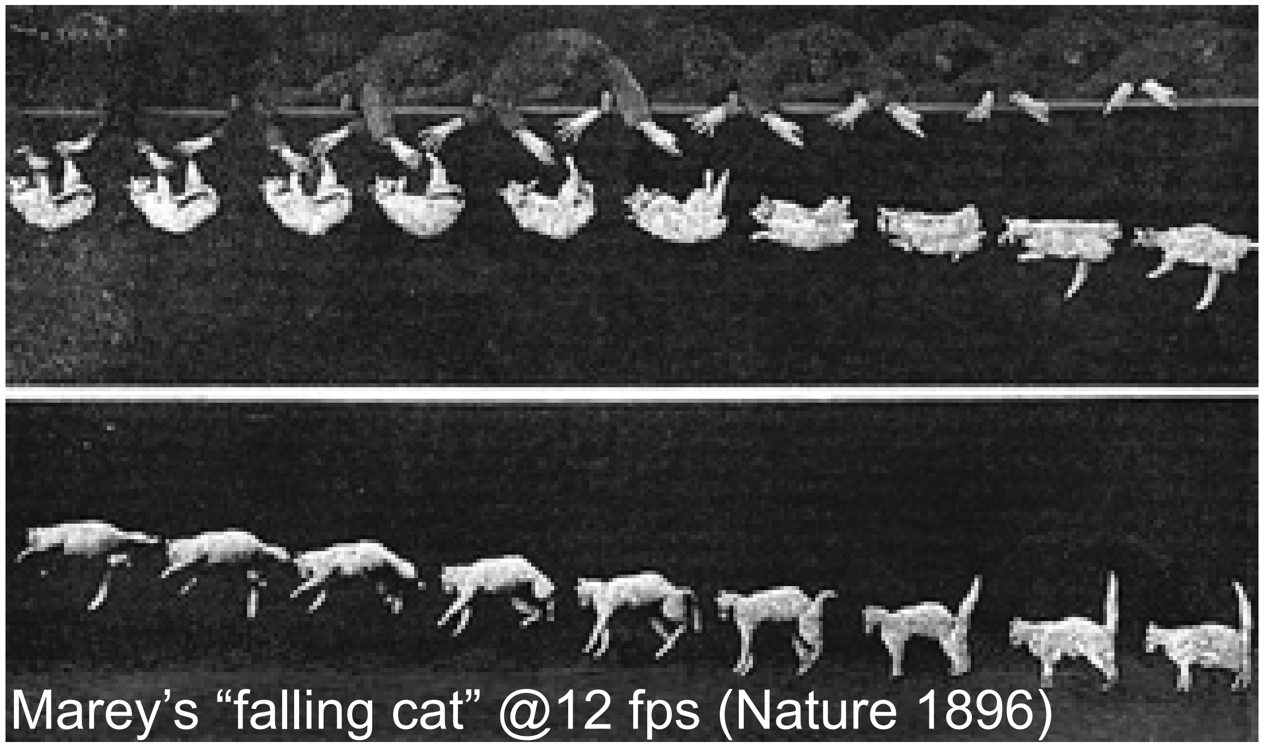
$$\Delta c = \int_0^T \dot{c}\; dt = \int_0^T \left[V_1(\xi(t))\dot{\xi}_1(t) + V_2(\xi(t))\dot{\xi}_2(t)\right] dt$$

$$= \oint [V_1(\xi)d\xi_1 + V_2(\xi)d\xi_2] = \int_\omega \mathrm{curl}_\xi V(\xi_1, \xi_2)\; d\xi_1 d\xi_2$$

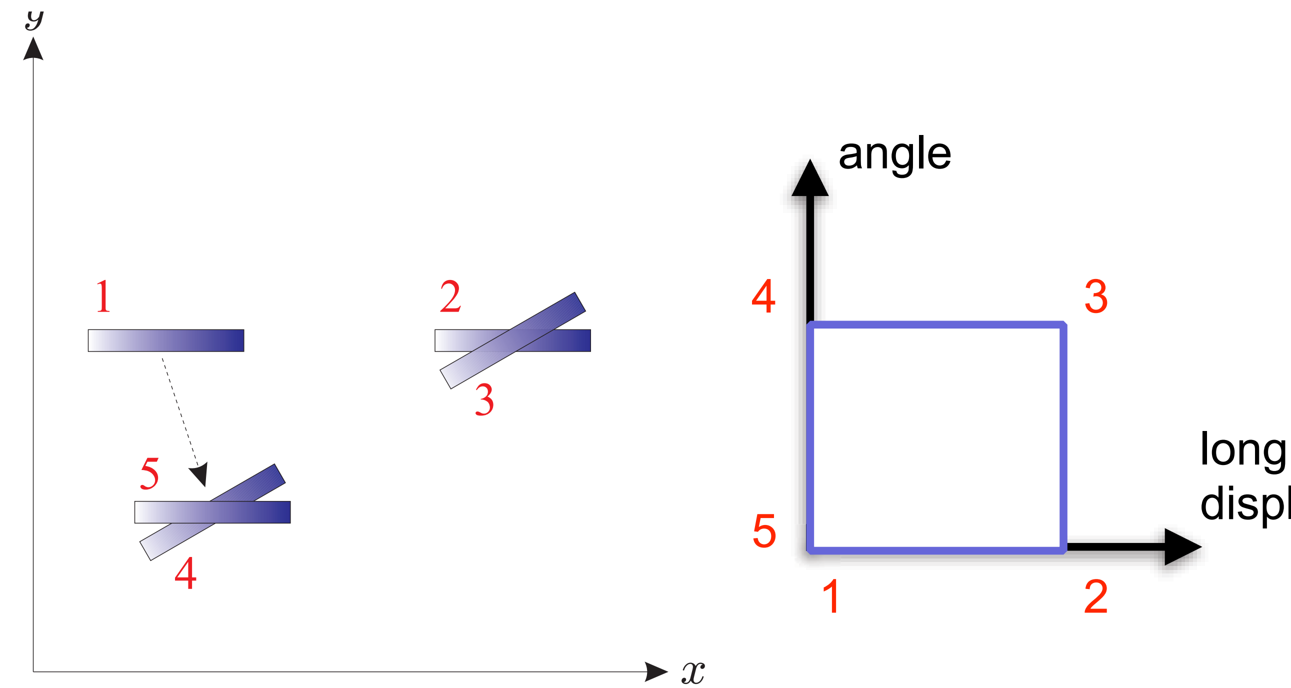


F. Alouges, A. DeSimone, JNLS'08

a minimal axisymmetric swimmer



Marey's "falling cat" @12 fps (Nature 1896)

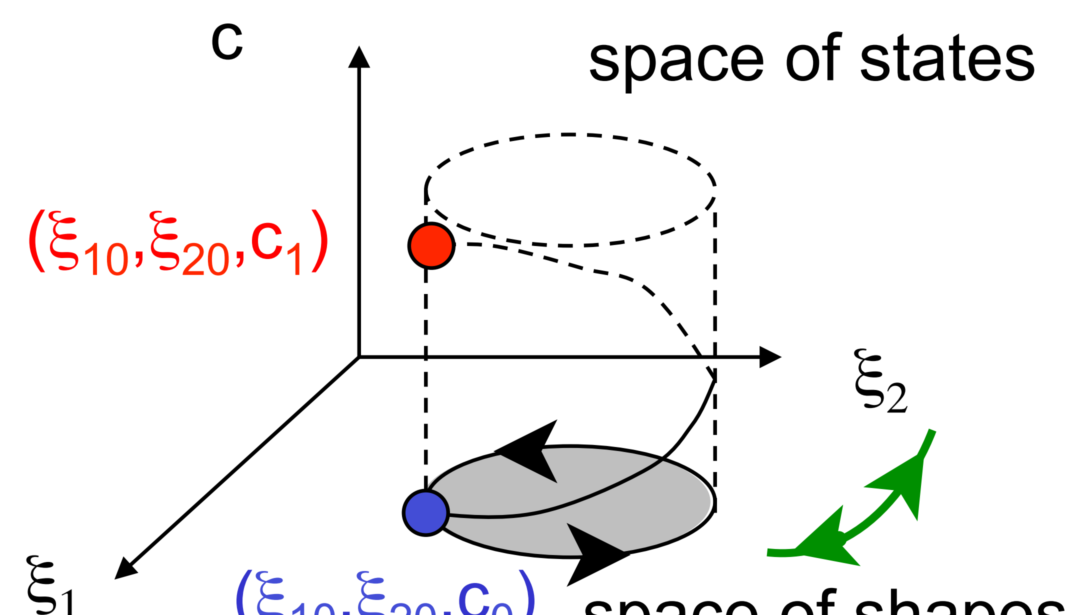


Parallel parking
(driving sidewise by looping of controlled dof's)

Motility map for 2 dof swimmer

$$\Delta c = \int_0^T \dot{c}\; dt = \int_0^T \left[V_1(\xi(t))\dot{\xi}_1(t) + V_2(\xi(t))\dot{\xi}_2(t) \right] dt$$

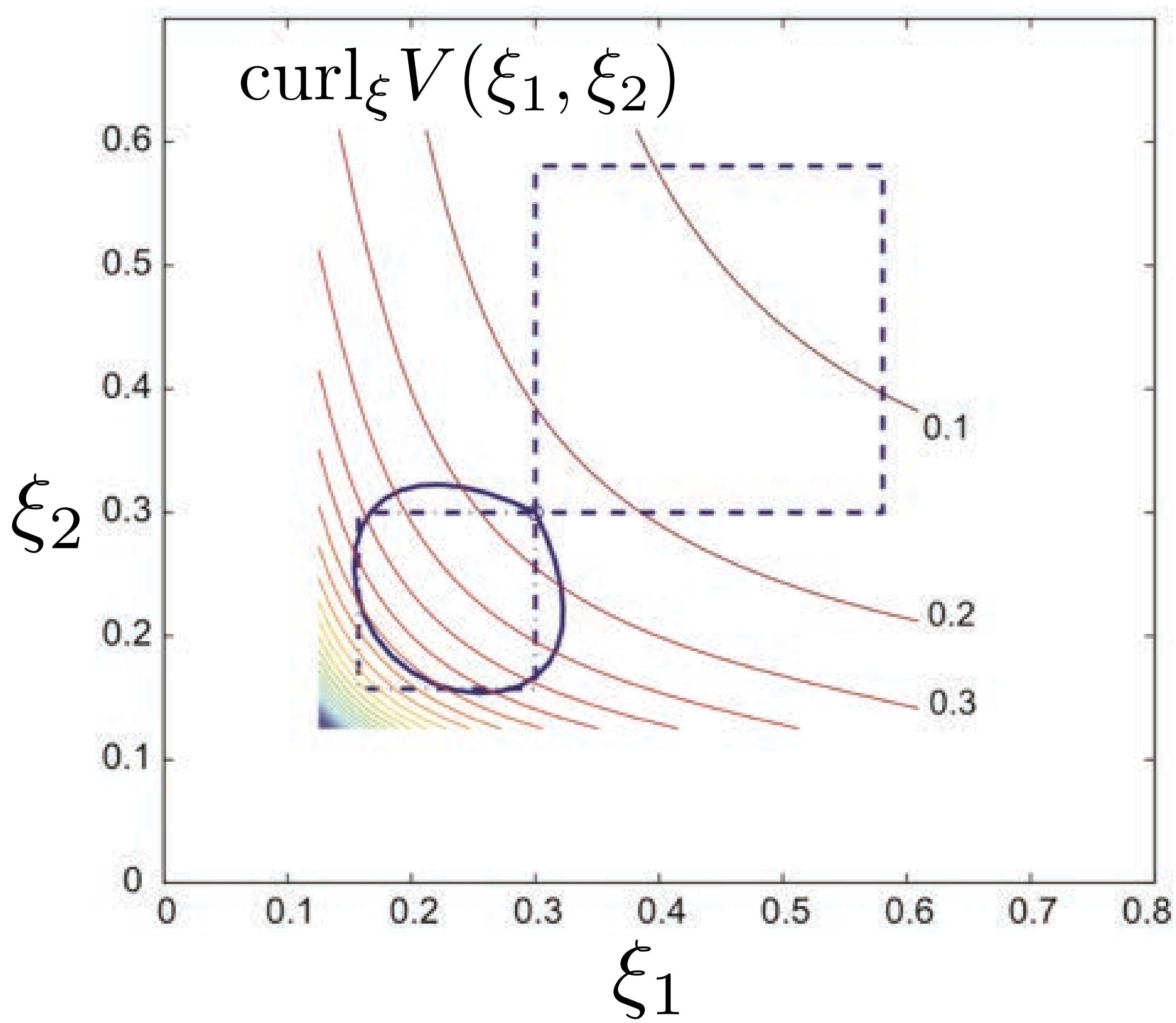
$$= \oint \left[V_1(\xi) d\xi_1 + V_2(\xi) d\xi_2 \right] = \int_\omega \mathrm{curl}_\xi V(\xi_1, \xi_2)\; d\xi_1 d\xi_2$$

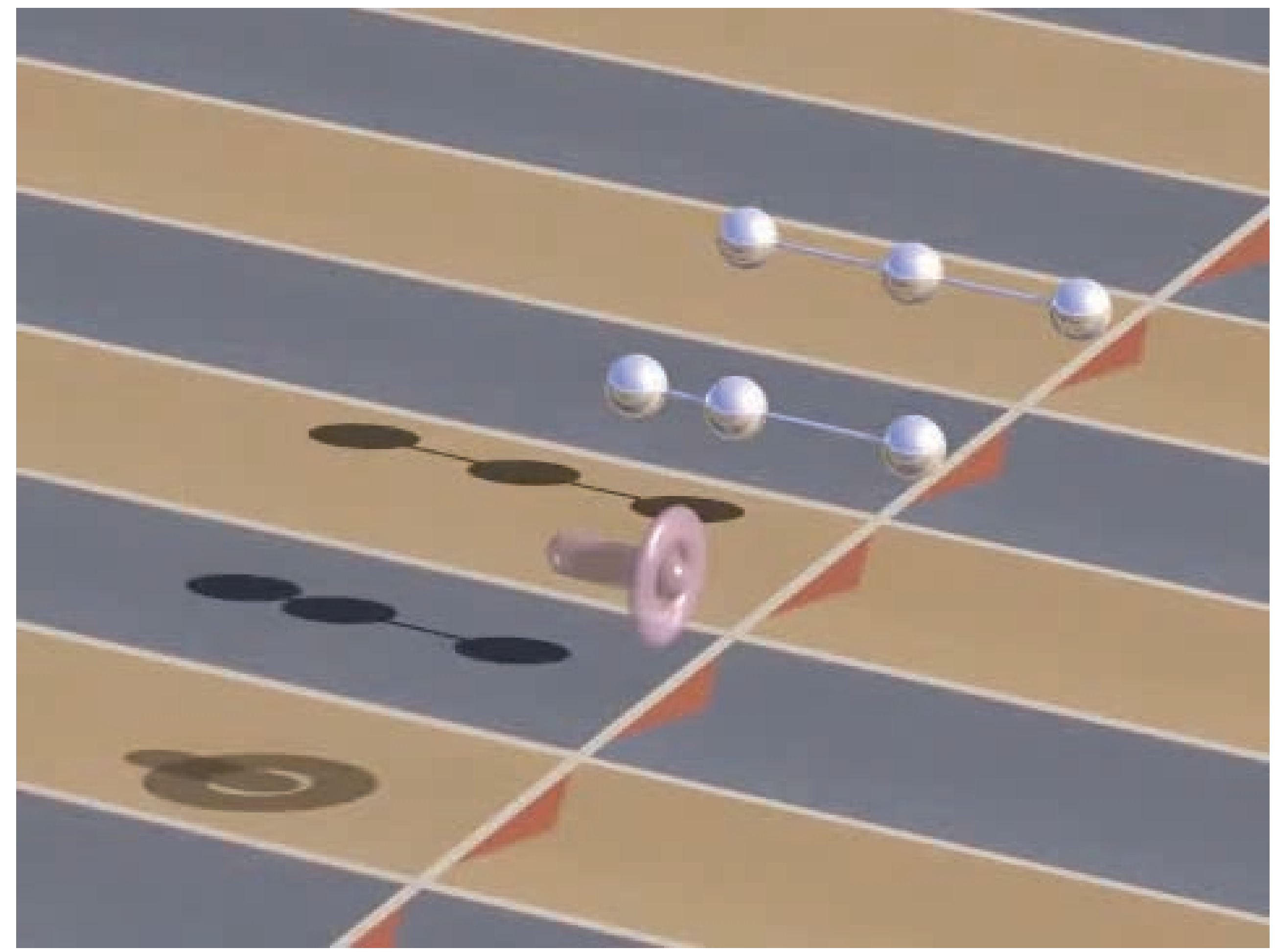


F. Alouges, A. DeSimone, JNLS'08

a minimal axisymmetric swimmer

Geometric framework provides a clear model for finding optimal strokes (e.g. those that dissipate the least energy in the fluid for a given Δc)

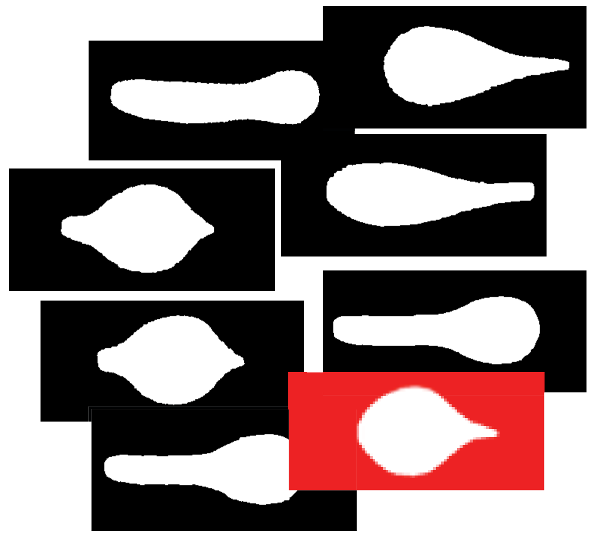




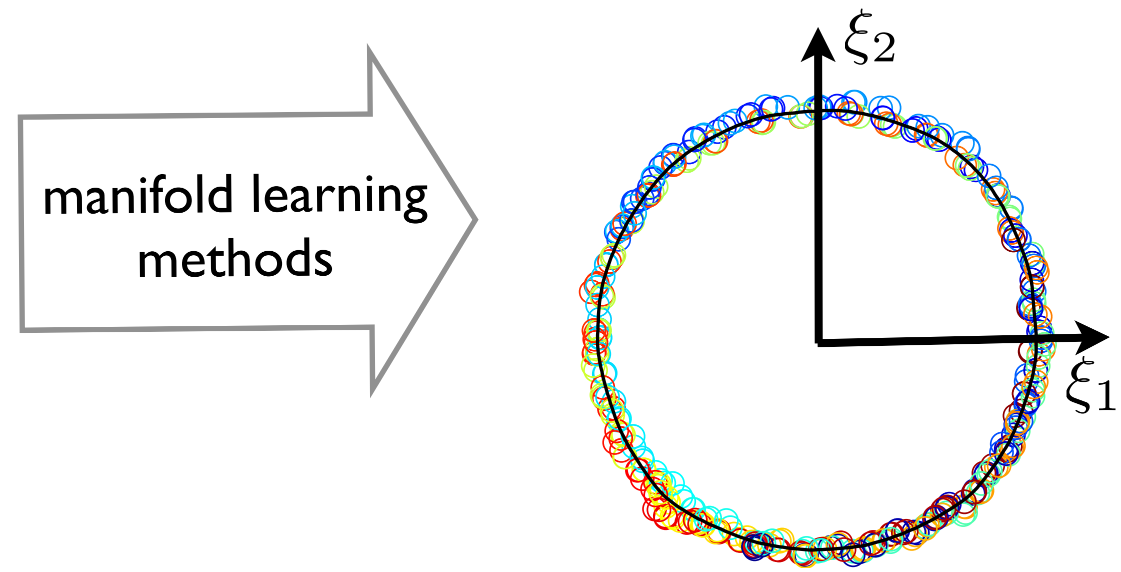
optimal Stokesian robots

L.. Heltai, F. Alouges, A. DeSimone

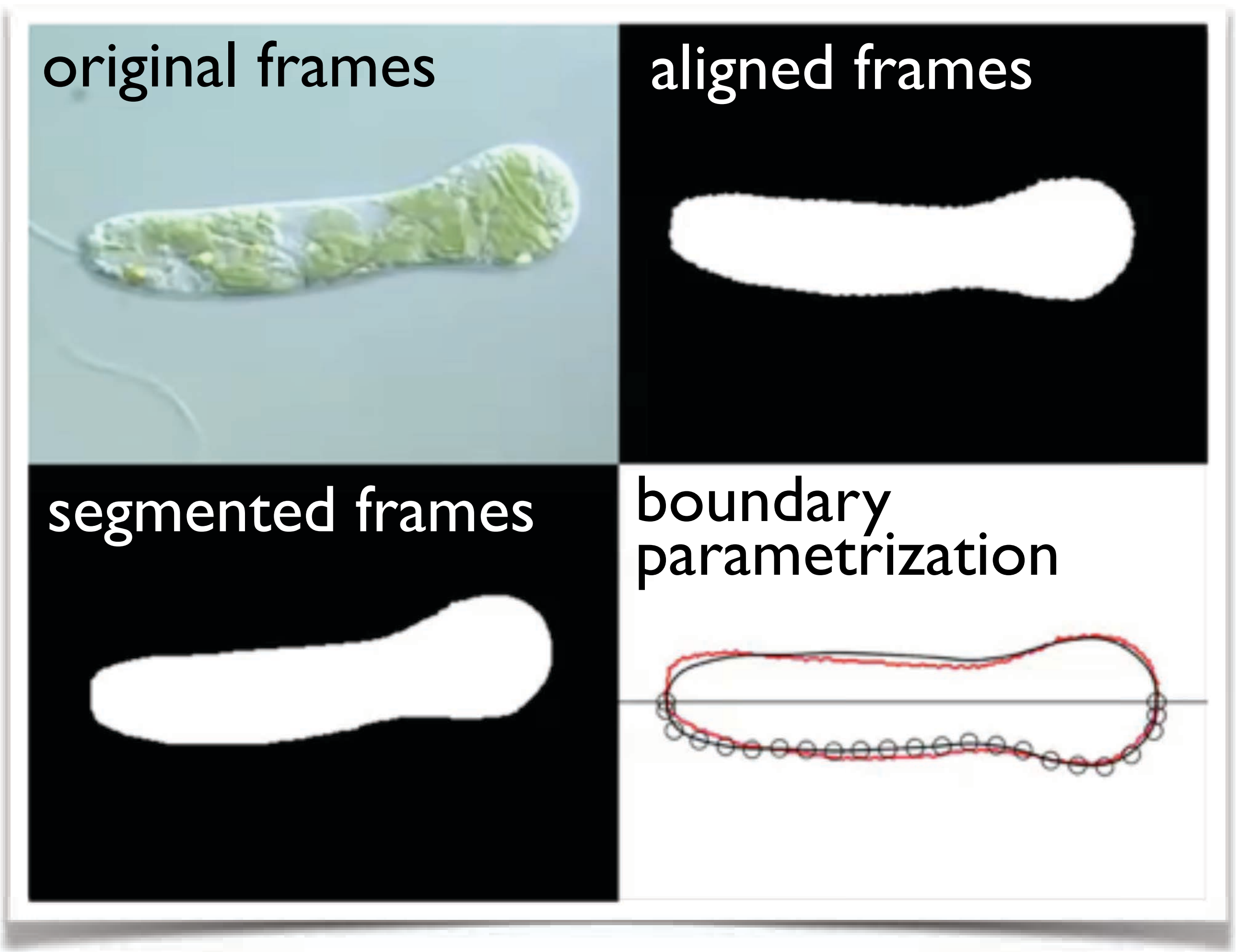
quantitative examination of euglena



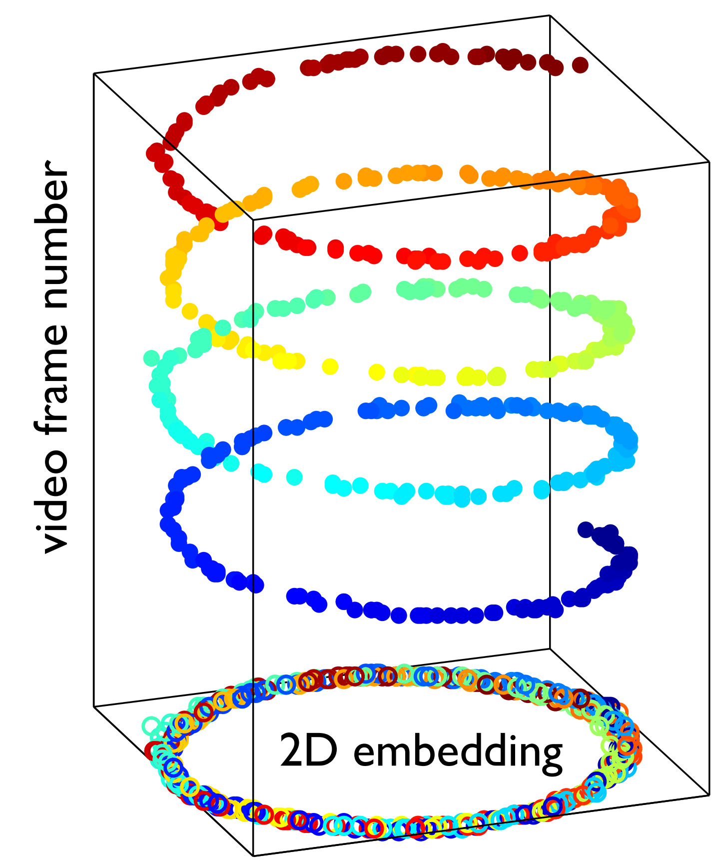
shape ensemble



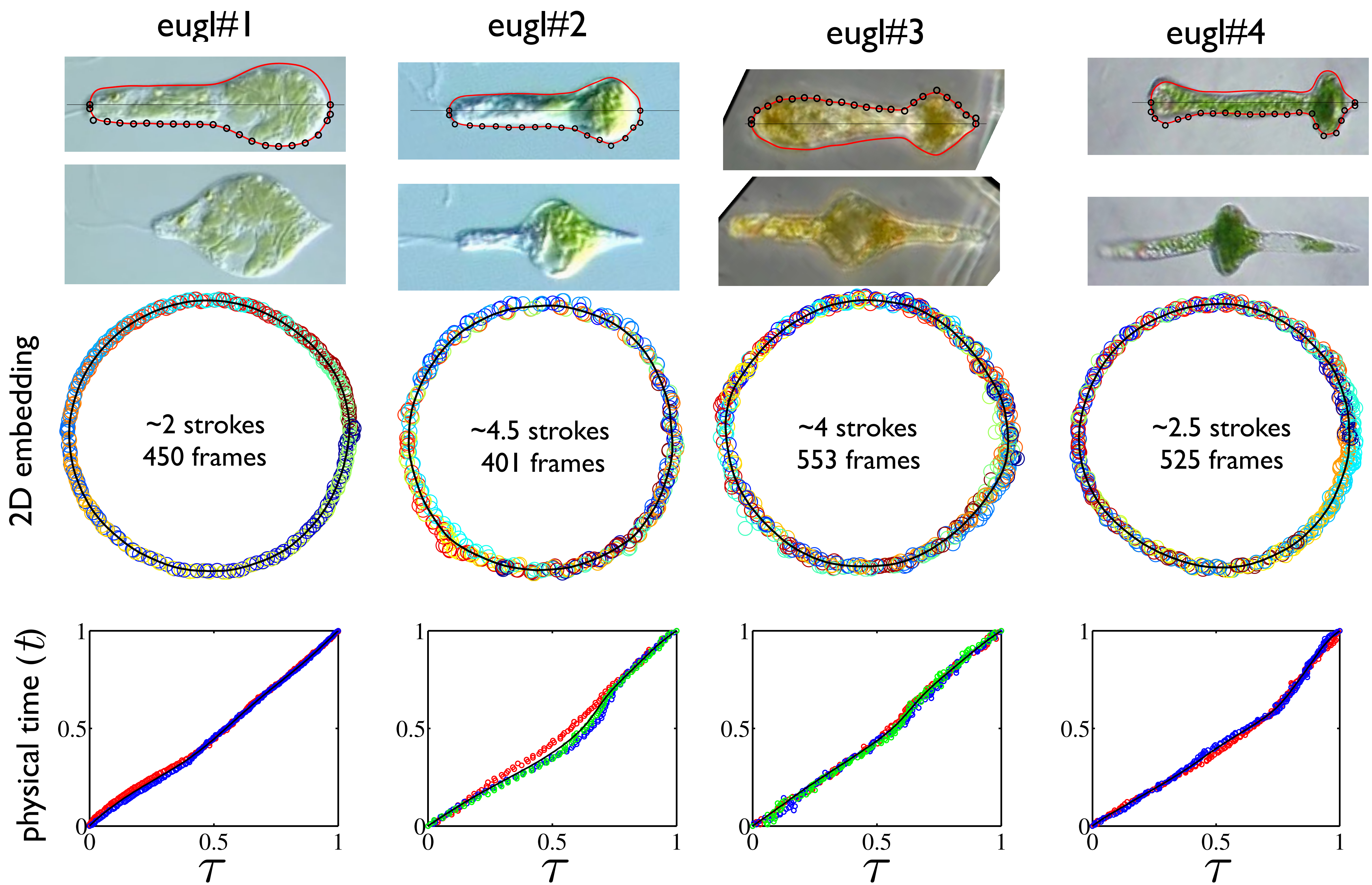
low-D embedding
~ ”shape space”



axisymmetric cells



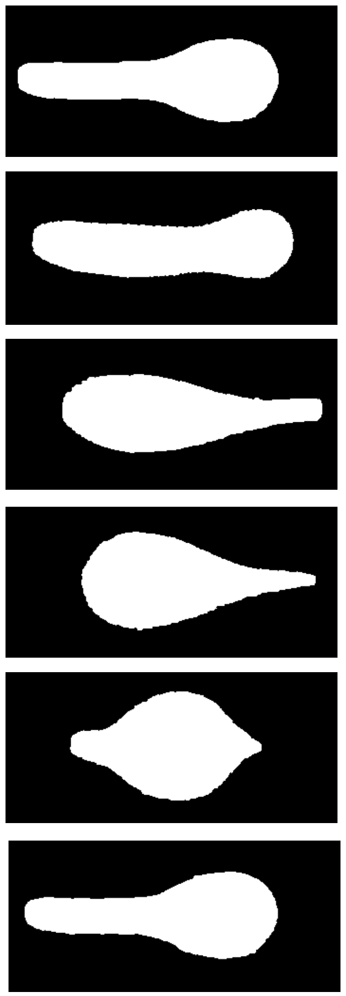
quantitative examination of euglena

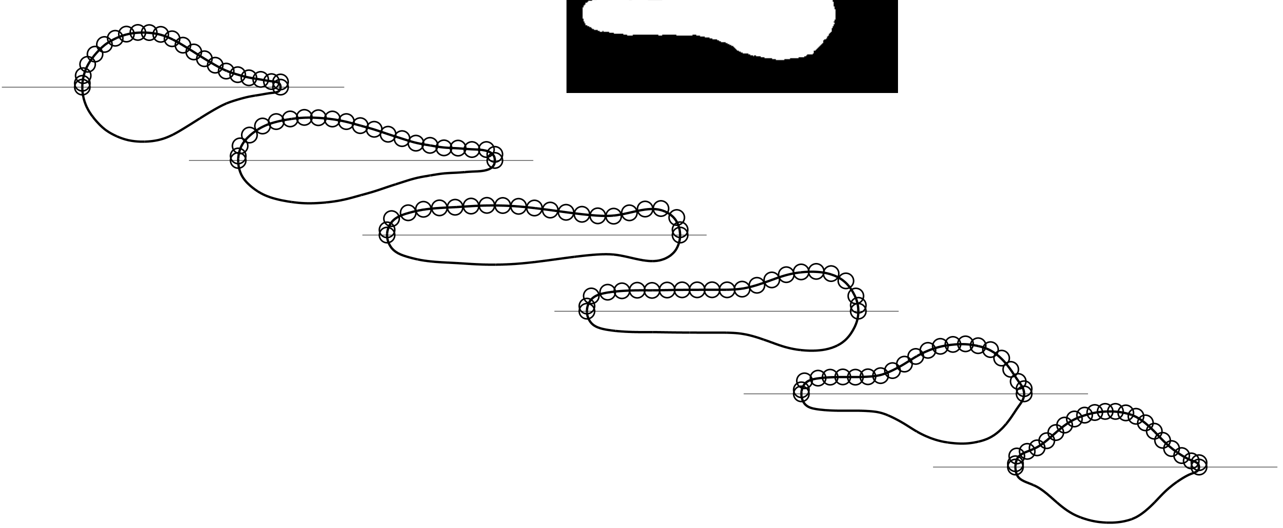


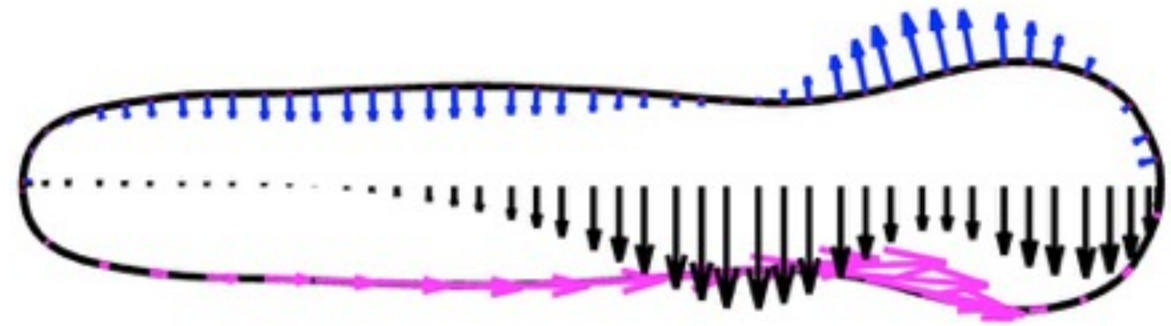
Non-reciprocal strokes highly reproducible in shape and pace

quantitative examination of euglena

Manifold learning algorithm also provides smooth numerical strokes that can be used in hydrodynamical calculations…

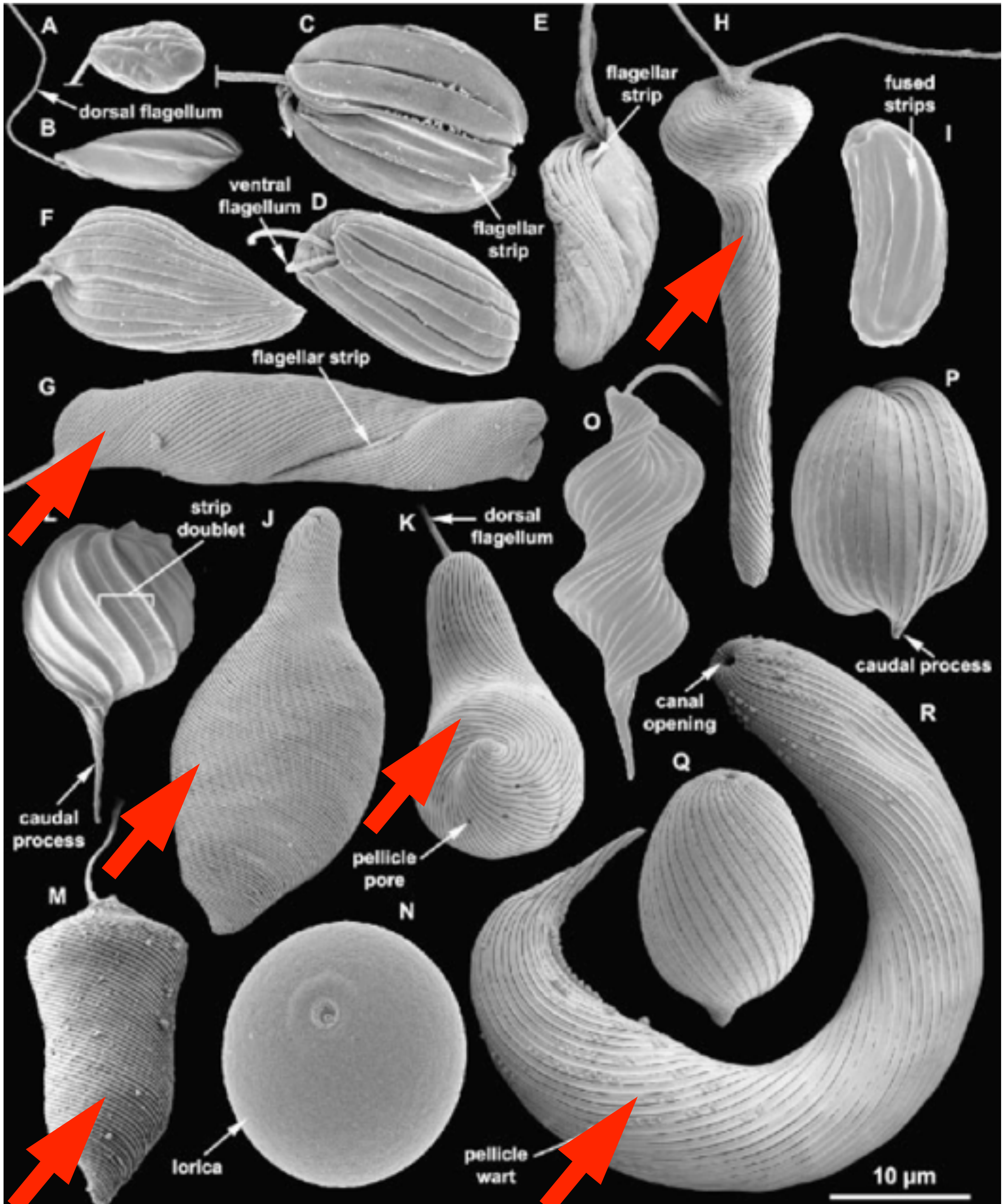






… but we only have information about normal velocity of the cell surface.

mechanism for shape actuation:

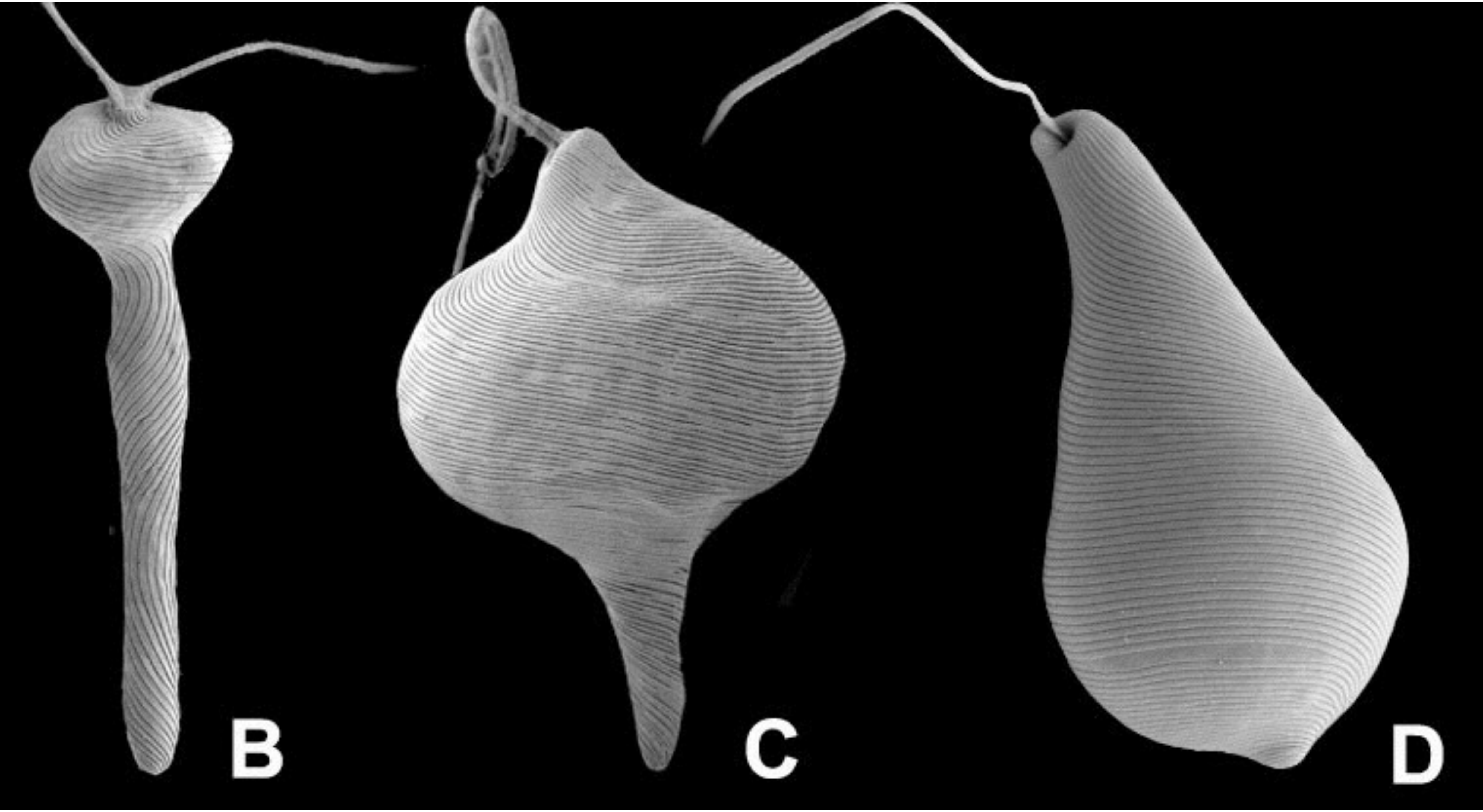


The pellicle is a striated envelop present in most euglenid species.

A large number of strips (10s) is correlated with pellicle plasticity.

B.S. Leander. Euglenids. tree of life web project., 2008

mechanism for shape actuation:



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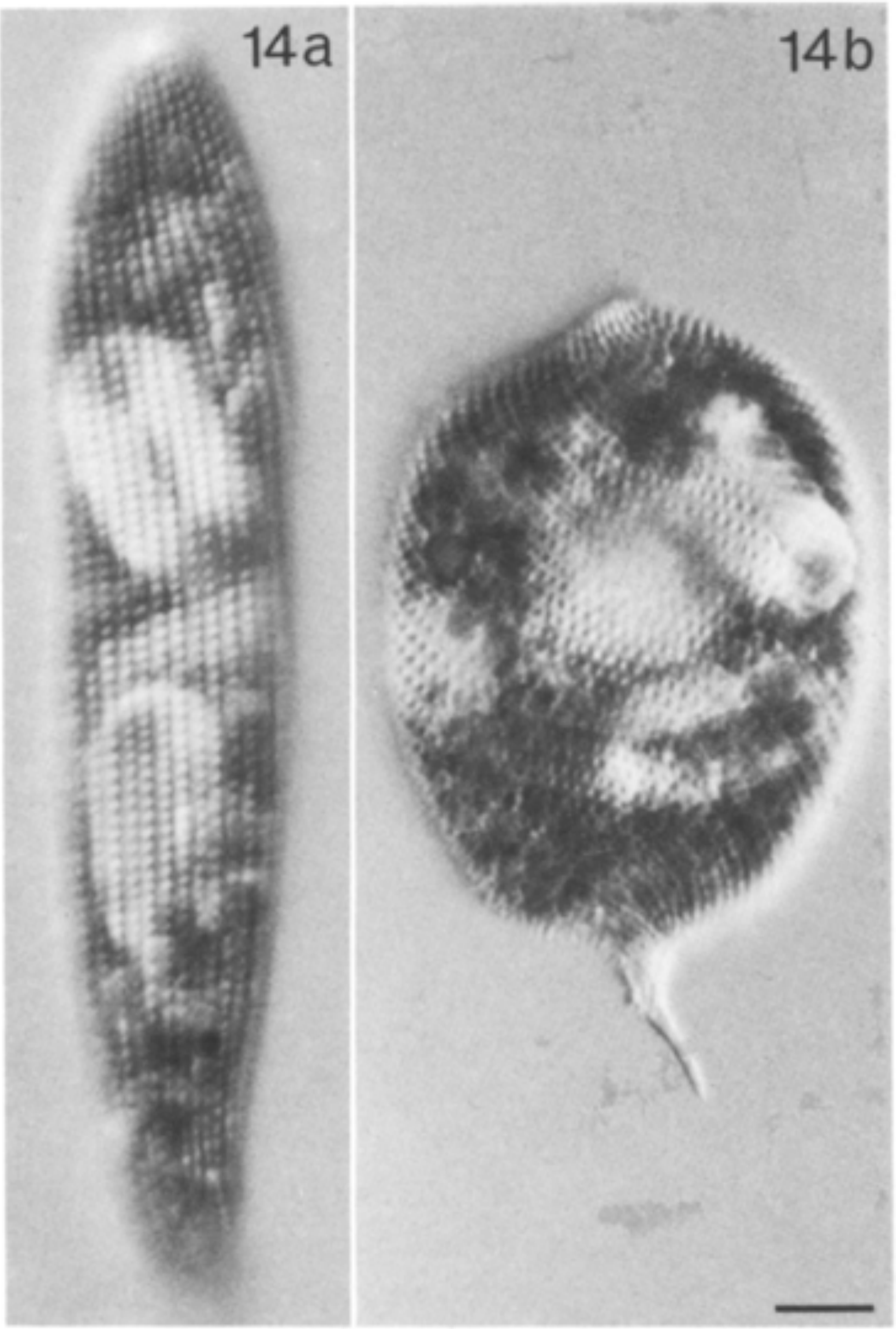
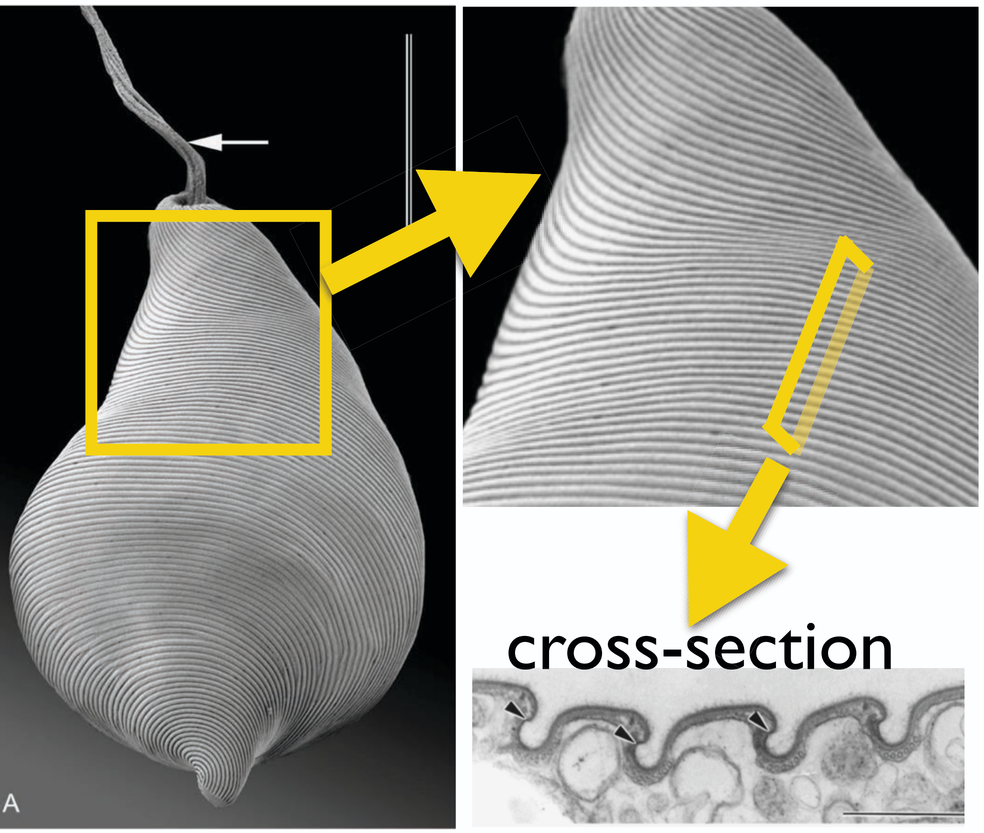
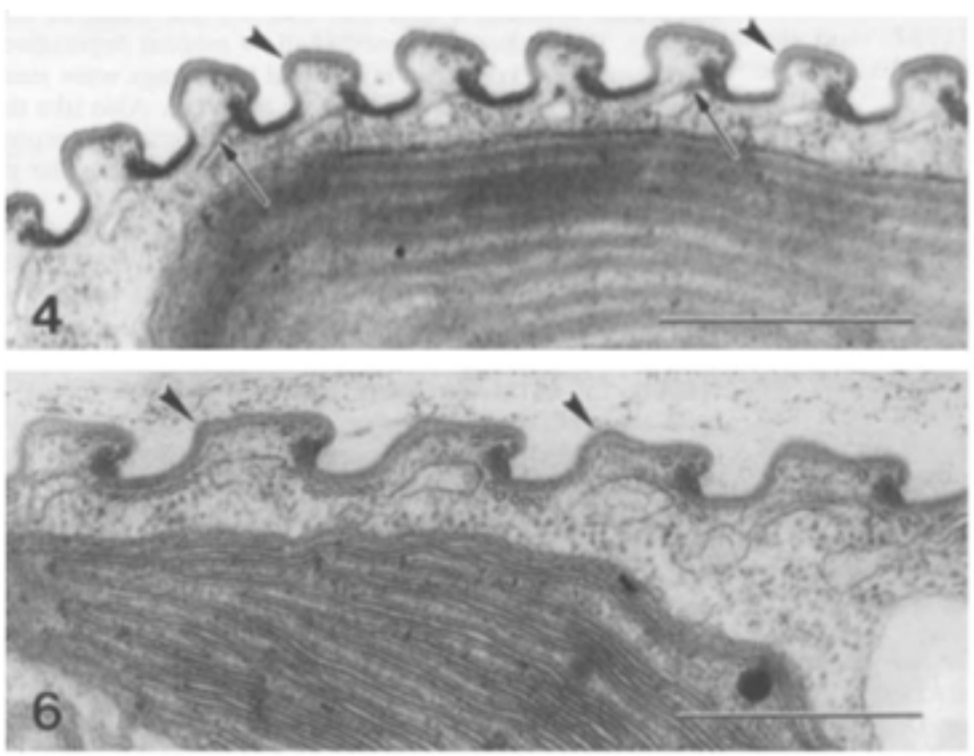


Suzaki, Williamson'85,'86

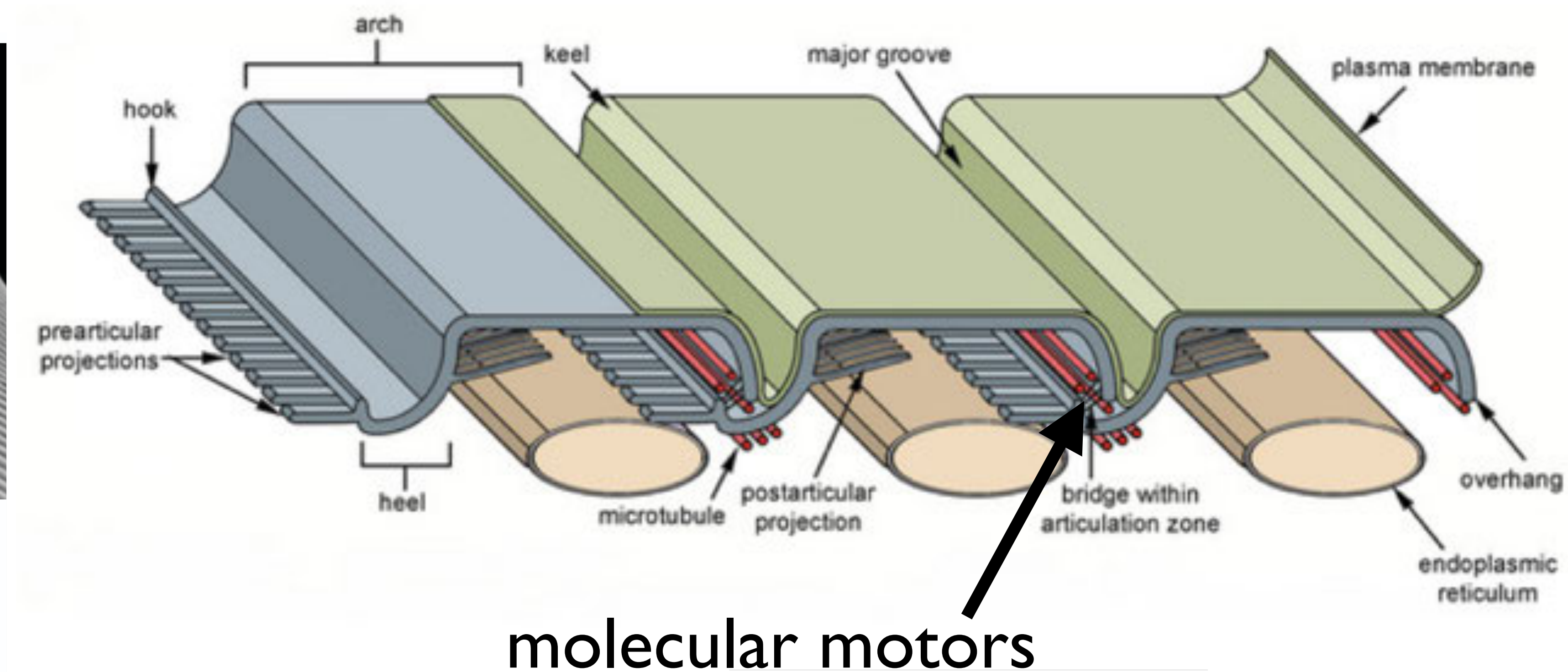
correlation between shape and pellicle configuration

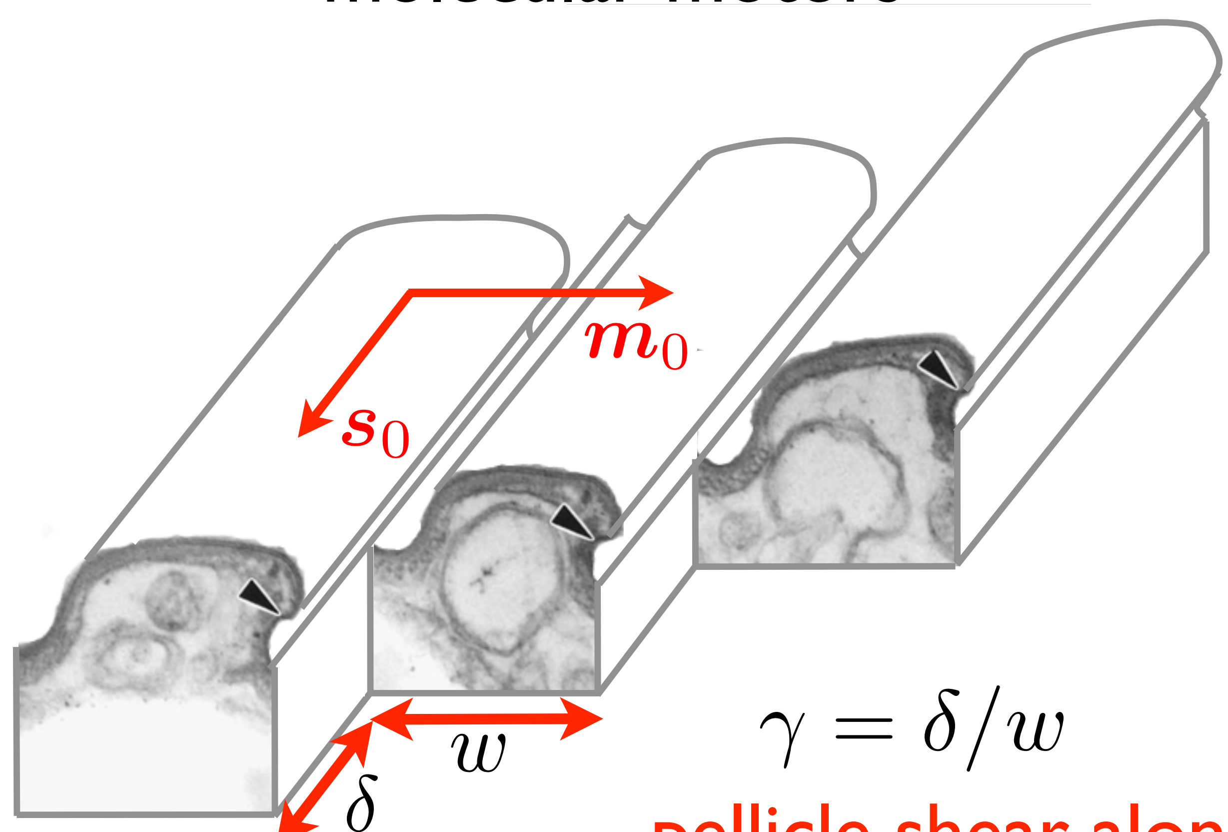
mechanism for shape actuation: the pellicle is the machine





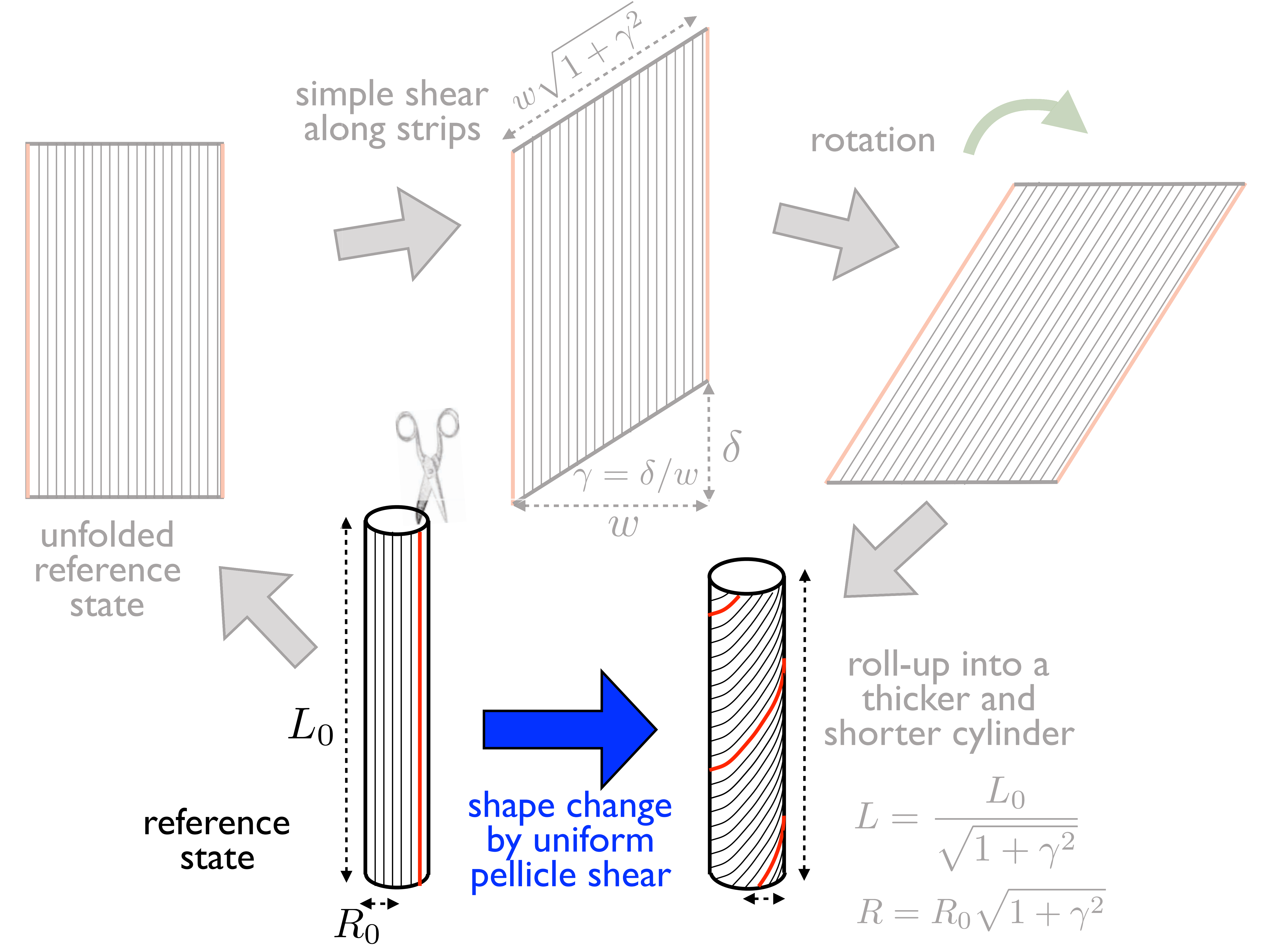
Leander, Farmer, 2001





$$\gamma = \delta / w$$

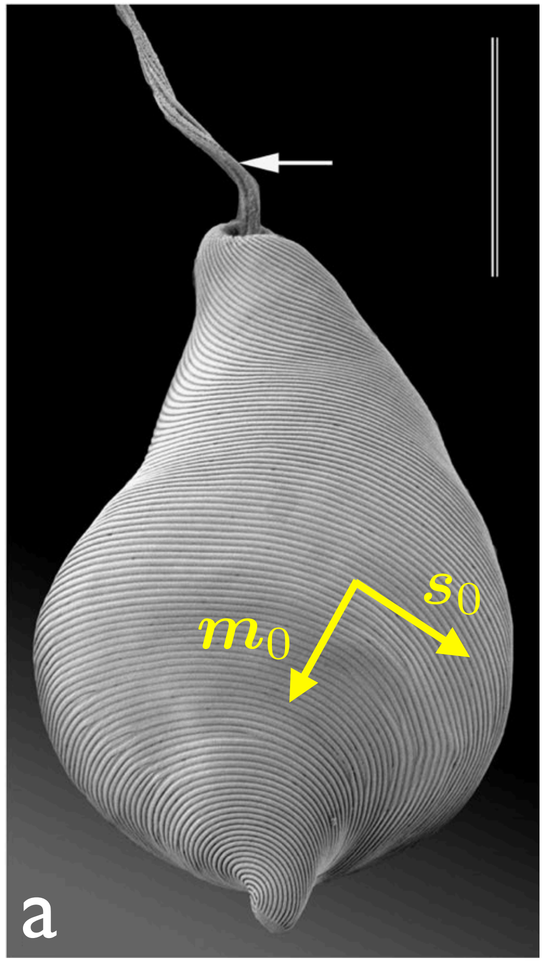
pellicle shear along strip direction



simple shear along strips
$w\sqrt{1+\gamma^2}$
rotation
δ
$\gamma = \delta/w$
w
unfolded reference state
roll-up into a thicker and shorter cylinder
L_0
$L = \frac{L_0}{\sqrt{1+\gamma^2}}$
reference state
shape change by uniform pellicle shear
$R = R_0\sqrt{1+\gamma^2}$
R_0

modeling the pellicle kinematics

More general shapes can be obtained if γ is not uniform:



Given a field of pellicle shears, **the local deformation (metric tensor)** of the surface is

$$\boldsymbol{C} = \boldsymbol{Id} + \gamma\left(\boldsymbol{s}_0 \otimes \boldsymbol{m}_0 + \boldsymbol{m}_0 \otimes \boldsymbol{s}_0\right) + \gamma^2 \boldsymbol{m}_0 \otimes \boldsymbol{m}_0 \quad (1)$$

On the other hand, given a deformed configuration $\boldsymbol{x}(u,v)$ the local deformation can be written as

$$C_{IJ} = g_{IJ} = \boldsymbol{x}_{,I} \cdot \boldsymbol{x}_{,J} \qquad (2)$$

"Forward problem": given $\gamma(u,v)$, find an isometric embedding of the metric tensor in (1)—the *target metric*.

"Inverse problem": given $\boldsymbol{x}(u,v)$, find the pellicle shear $\gamma(u,v)$ such that (1) and (2) agree.

modeling the pellicle kinematics

"Forward problem": given $\gamma(u,v)$, find an isometric embedding of the metric tensor in (1)—the *target metric.*

$$\boldsymbol{C} = \boldsymbol{Id} + \gamma\left(\boldsymbol{s}_0 \otimes \boldsymbol{m}_0 + \boldsymbol{m}_0 \otimes \boldsymbol{s}_0\right) + \gamma^2 \boldsymbol{m}_0 \otimes \boldsymbol{m}_0 \quad (1)$$

Simplifying the equations for a cylindrical pellicle with straight strips:

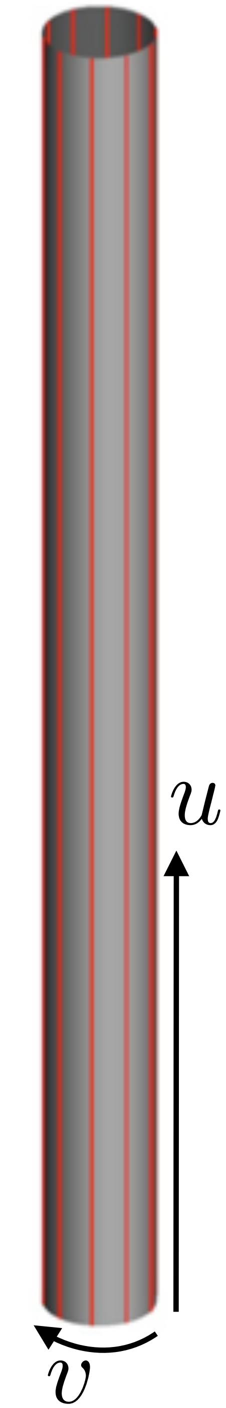
$$\begin{bmatrix} \boldsymbol{x}_{,u} \cdot \boldsymbol{x}_{,u} & \boldsymbol{x}_{,u} \cdot \boldsymbol{x}_{,v} \\ \boldsymbol{x}_{,u} \cdot \boldsymbol{x}_{,v} & \boldsymbol{x}_{,v} \cdot \boldsymbol{x}_{,v} \end{bmatrix} = \begin{bmatrix} 1 & \gamma \\ \gamma & 1+\gamma^2 \end{bmatrix}$$

$$K = (\gamma_{,v} - \gamma\gamma_{,u})_{,u}$$

Pellicle shear induces non-Euclidean geometry.

Global existence of solutions to this system of nonlinear PDE cannot be expected, and if solutions exist they may be non-unique.

Equations changes character with sign of K



modeling the pellicle kinematics

non-Euclidean geometry induced by growth

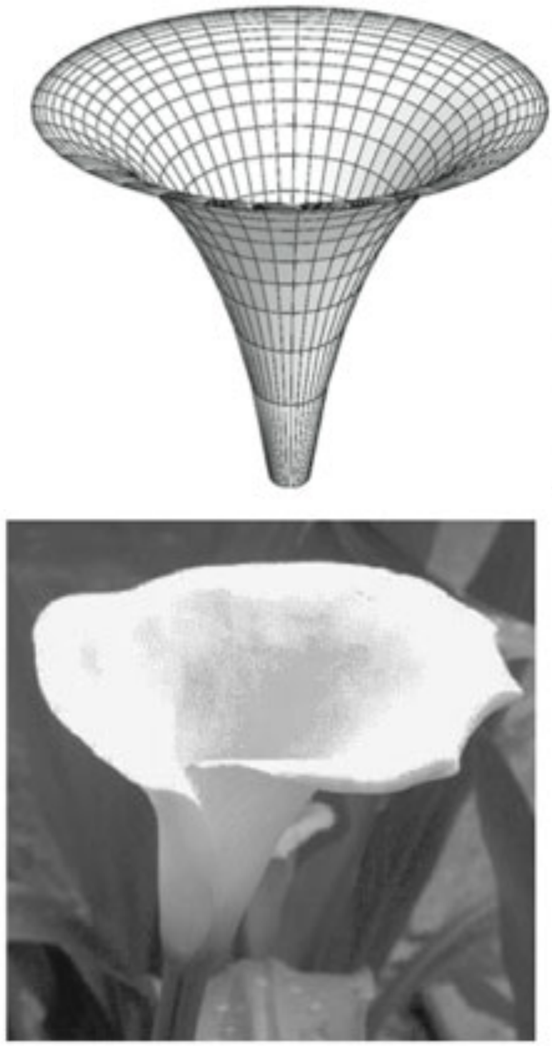
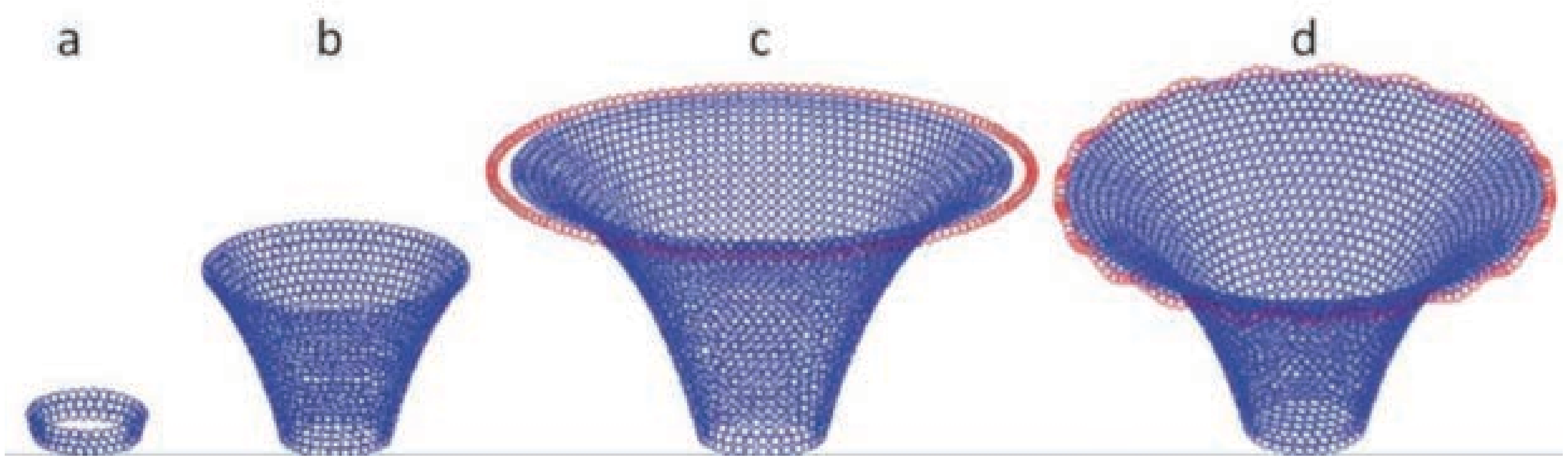


Figure 2. (*a*) Pseudosphere. (*b*) Picture of a calla lilly.

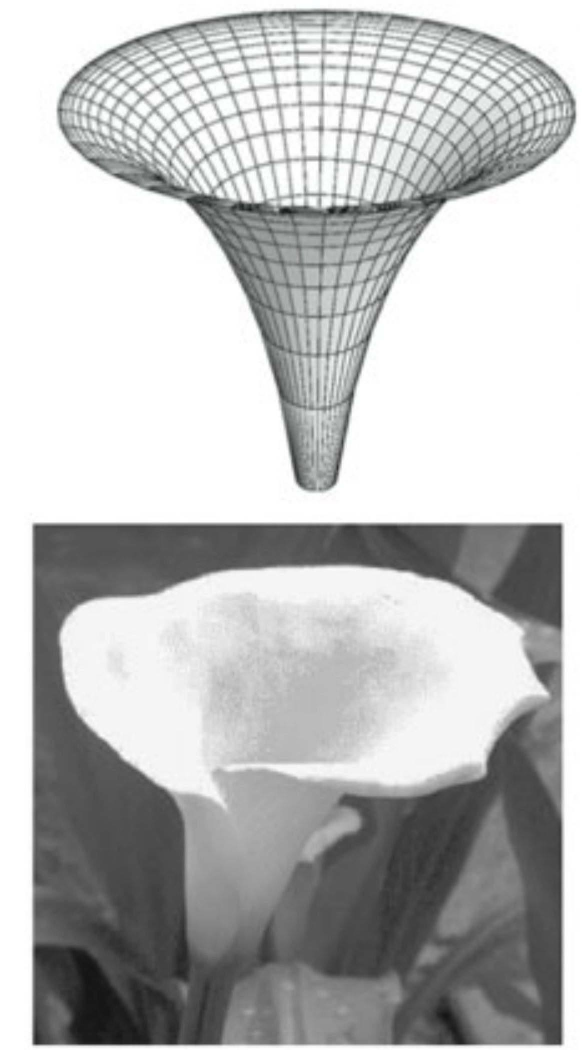
Nechaev, Voituriez'01



This geometrical model works because generically thin films are easy to bend but very difficult to stretch.

modeling the pellicle kinematics

non-Euclidean geometry induced by growth



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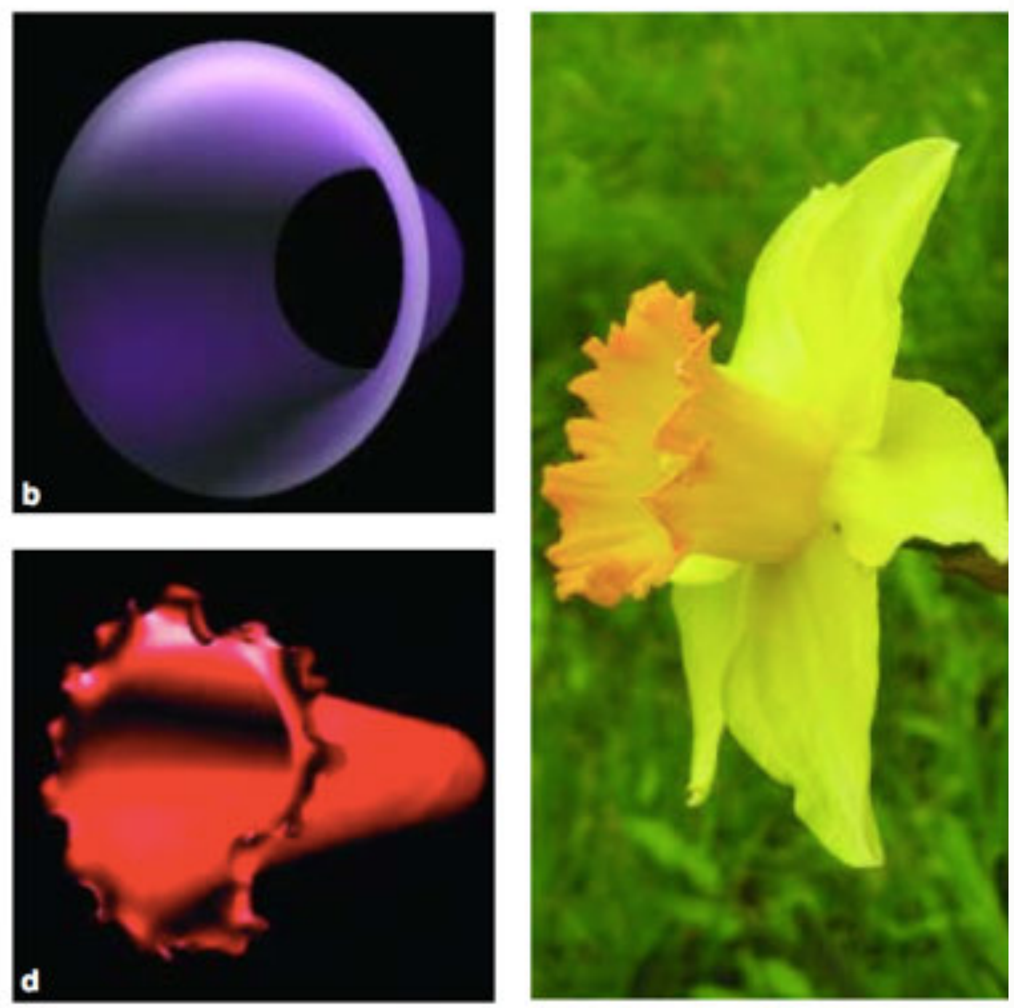
Nechaev, Voituriez'01



Sharon, Marder, Swinney'04

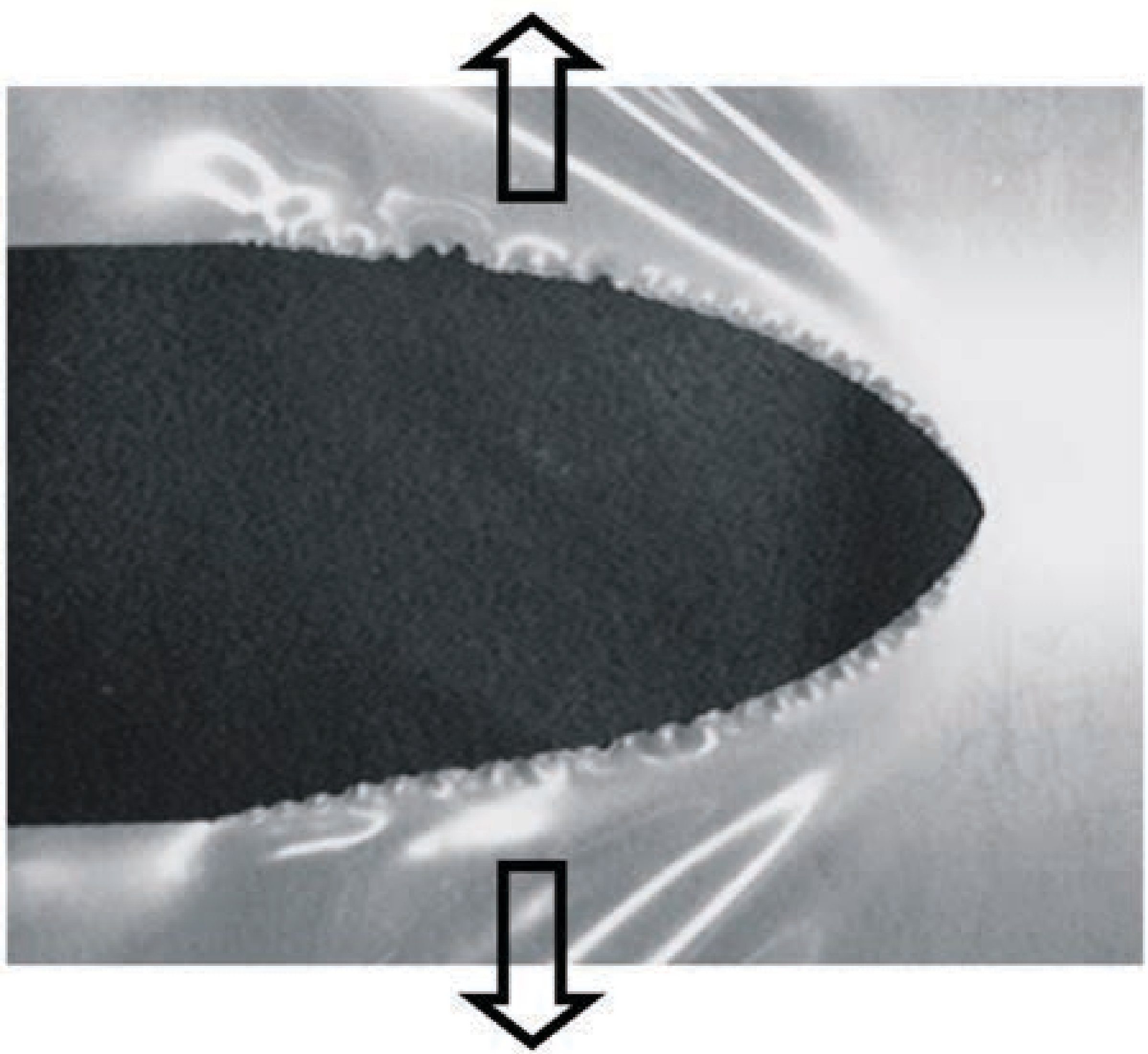
Mahadevan, Liang'10

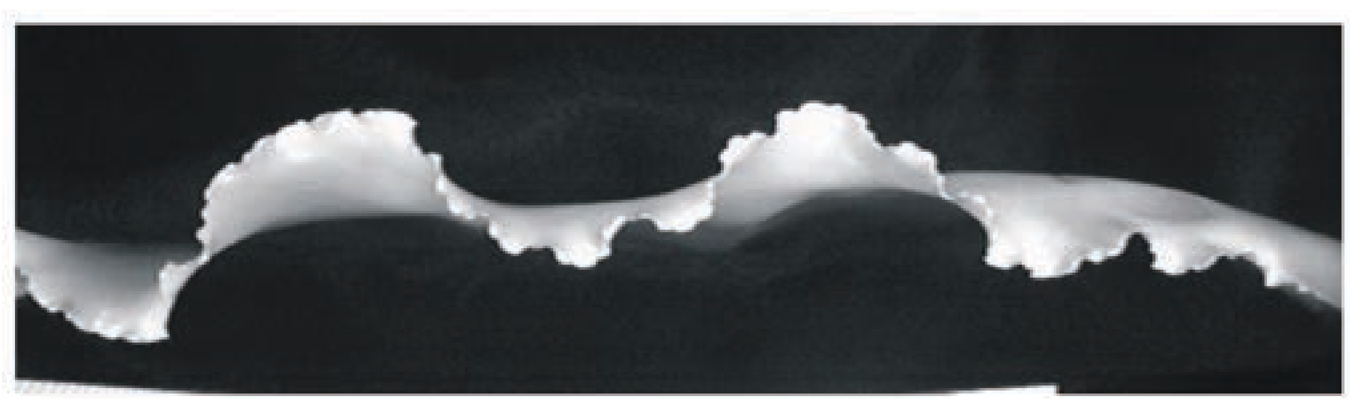
This geometrical model works because generically thin films are easy to bend but very difficult to stretch.

modeling the pellicle kinematics

non-Euclidean geometry induced by plastic deformation

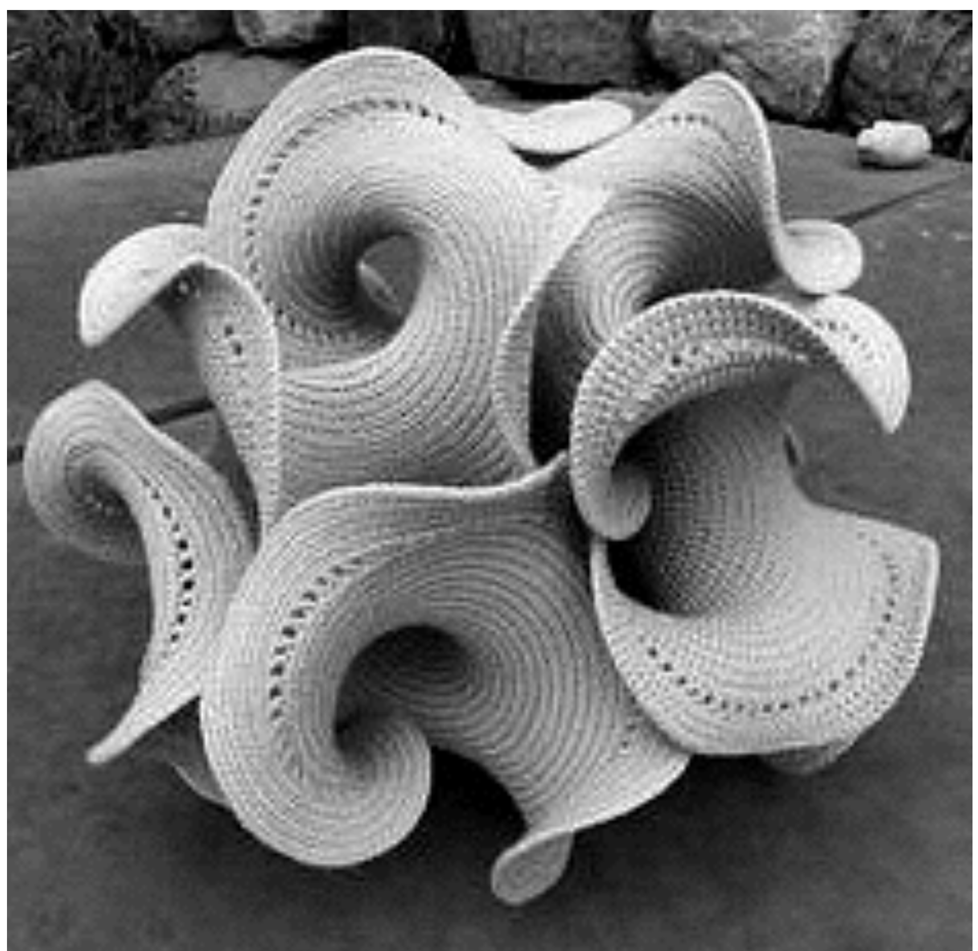
Plastic deformation





modeling the pellicle kinematics

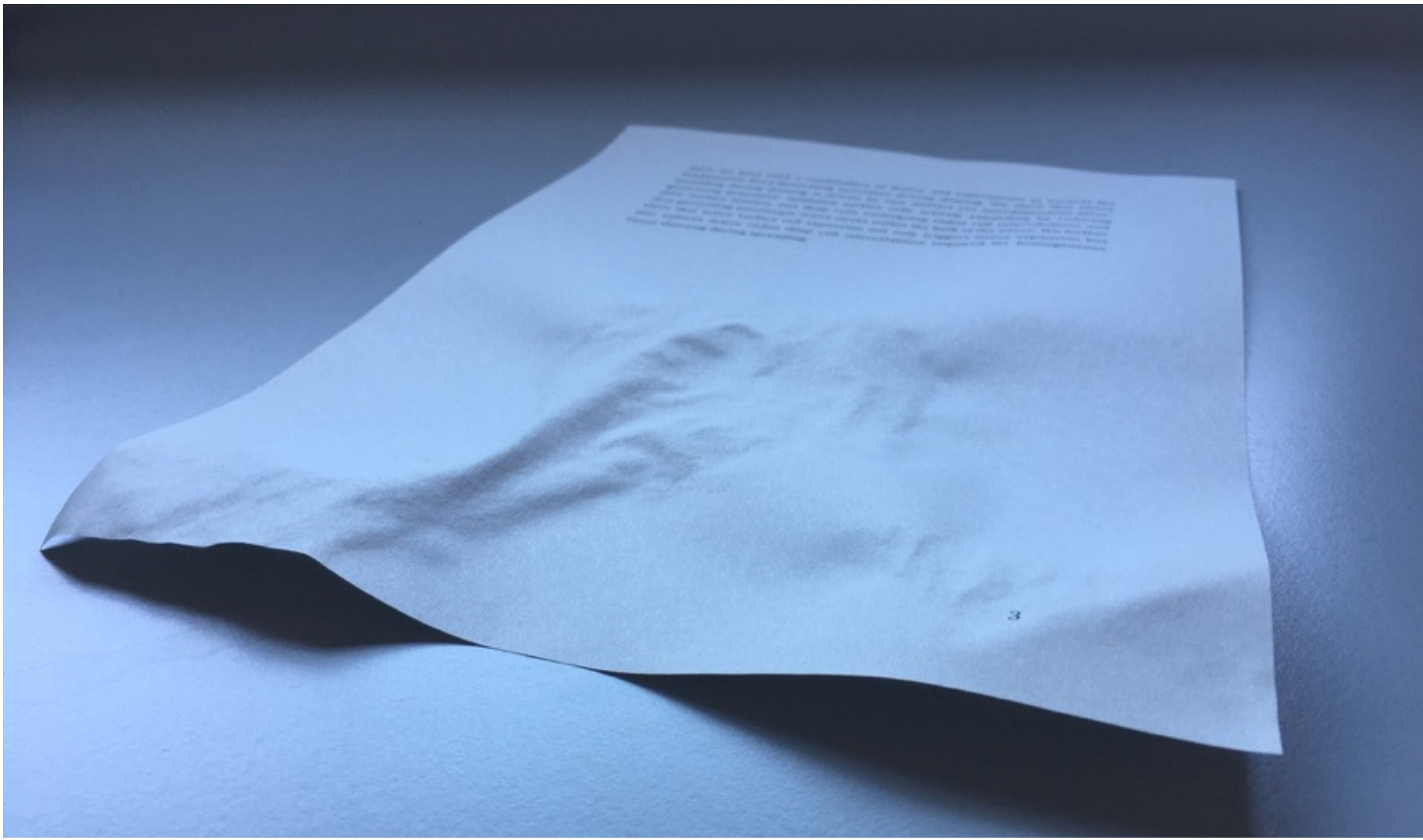
non-Euclidean geometry induced by crochet pattern



Gabriele Meyer

modeling the pellicle kinematics

non-Euclidean geometry induced by differential swelling

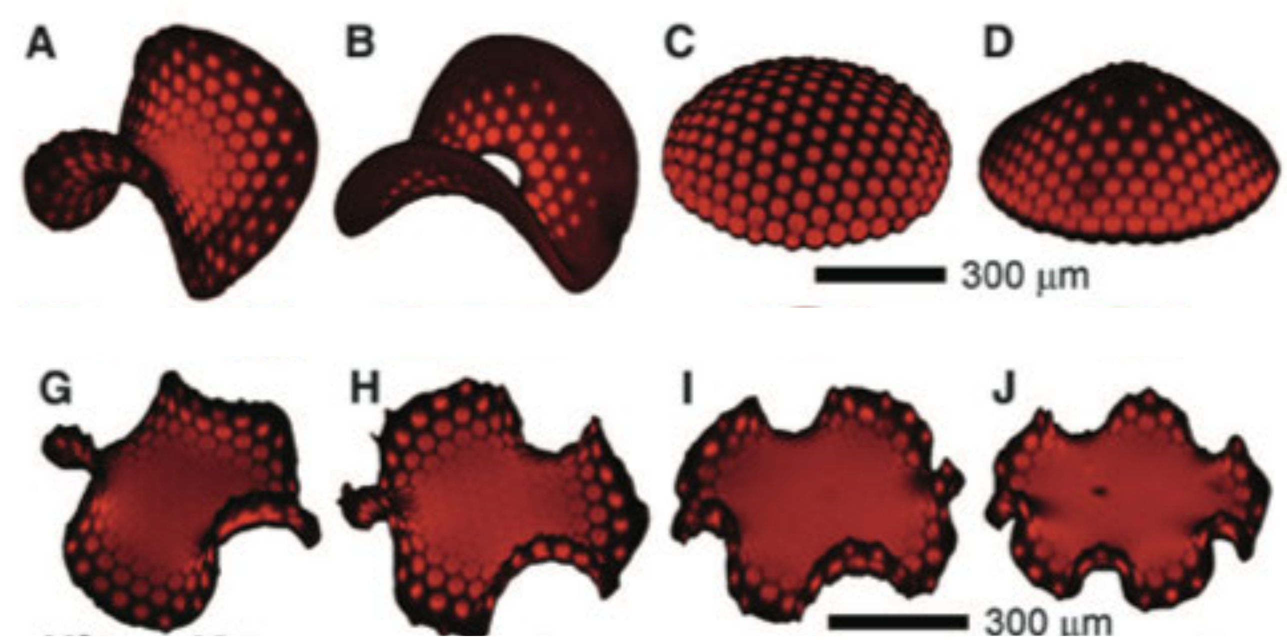


modeling the pellicle kinematics

non-Euclidean geometry induced by differential swelling

Klein, Efrati, Sharon, *Science*'07

programable soft materials



Kim et al, *Science*'12

modeling the pellicle kinematics

The forward problem (find isometric embedding)

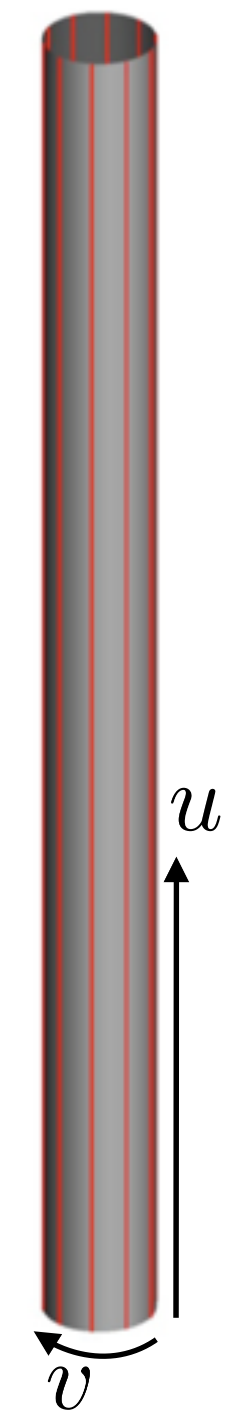
$$\begin{bmatrix} \boldsymbol{x}_{,u}\cdot\boldsymbol{x}_{,u} & \boldsymbol{x}_{,u}\cdot\boldsymbol{x}_{,v} \\ \boldsymbol{x}_{,u}\cdot\boldsymbol{x}_{,v} & \boldsymbol{x}_{,v}\cdot\boldsymbol{x}_{,v} \end{bmatrix} = \begin{bmatrix} 1 & \gamma \\ \gamma & 1+\gamma^2 \end{bmatrix}$$

Assuming axisymmetry $\gamma_{,v} = 0$

$$\begin{bmatrix} r'^2 + z'^2 + r^2\psi'^2 & r^2\psi'/R_0 \\ r^2\psi'/R_0 & (r/R_0)^2 \end{bmatrix} = \begin{bmatrix} 1 & \gamma \\ \gamma & 1+\gamma^2 \end{bmatrix}$$

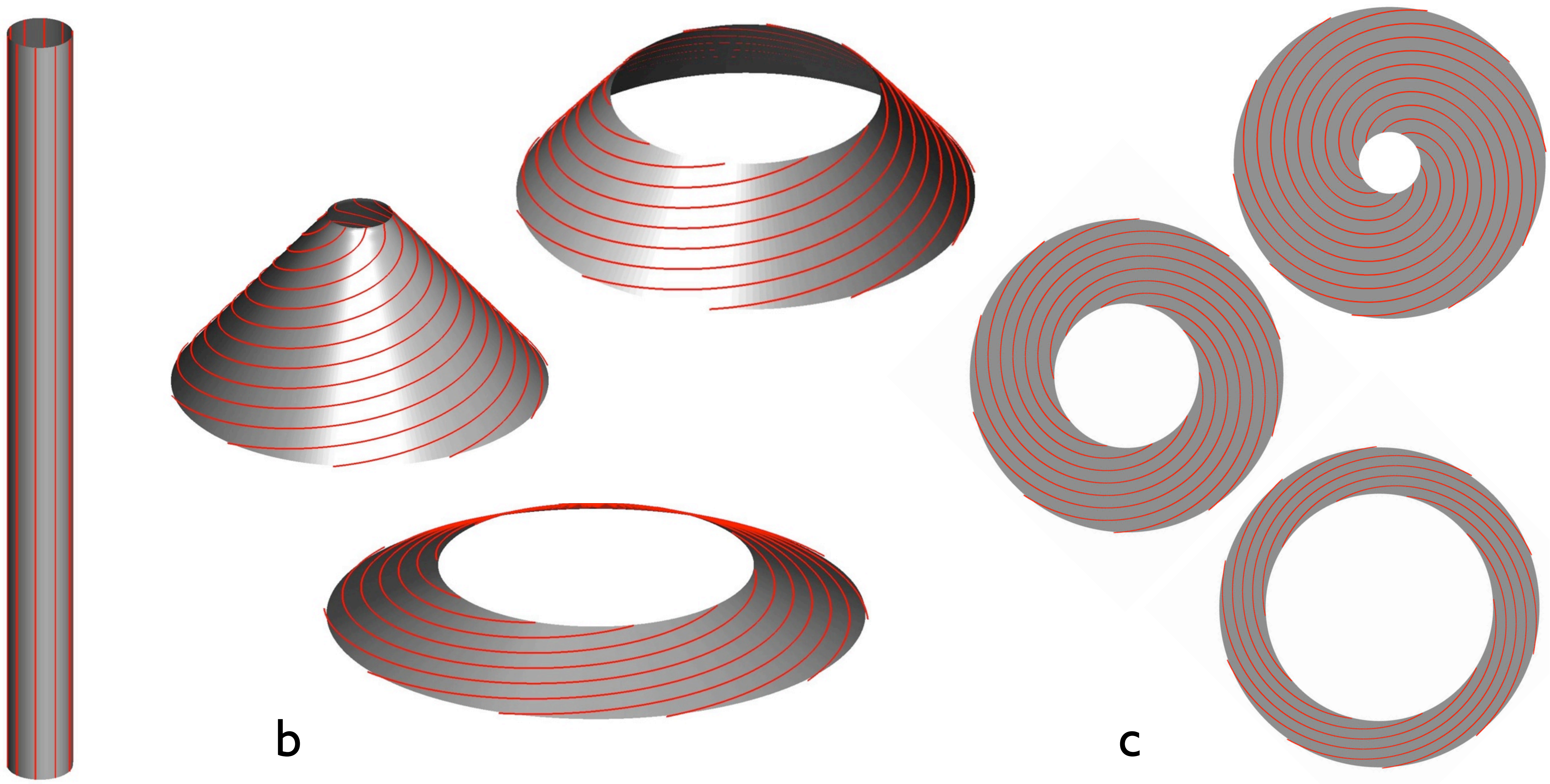
$$\begin{aligned} r(u) &= R_0\sqrt{1+\gamma^2}, \\ \psi'(u) &= \frac{\gamma}{R_0(1+\gamma^2)}, \\ z'(u) &= \sqrt{\frac{1-(R_0\gamma\gamma')^2}{1+\gamma^2}} \end{aligned}$$

Embeddability condition $|\gamma\gamma'| \leq 1/R_0$



modeling the pellicle kinematics

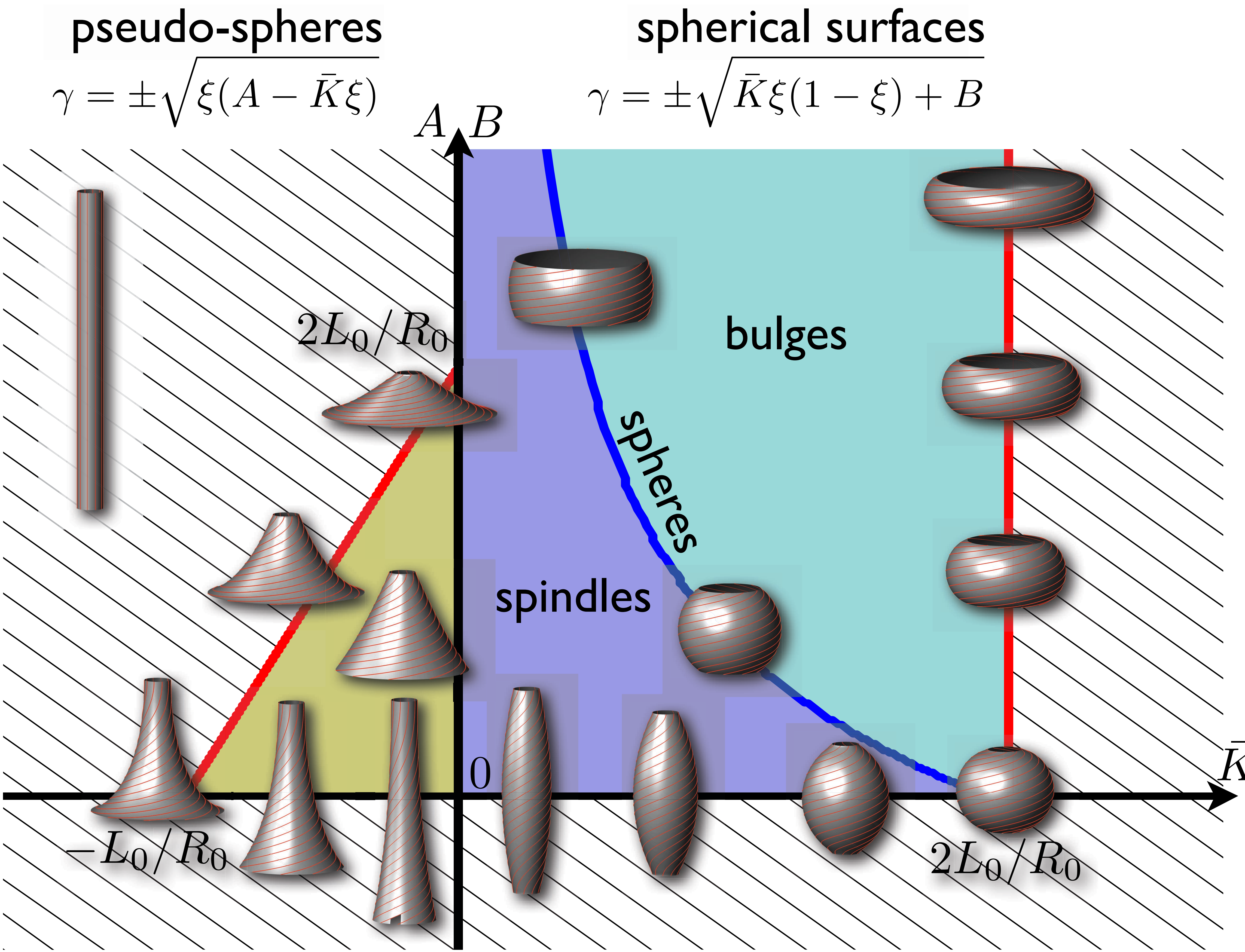
- K=0 $\gamma(u) = \sqrt{A(1-\xi) + B\xi}$



a b c

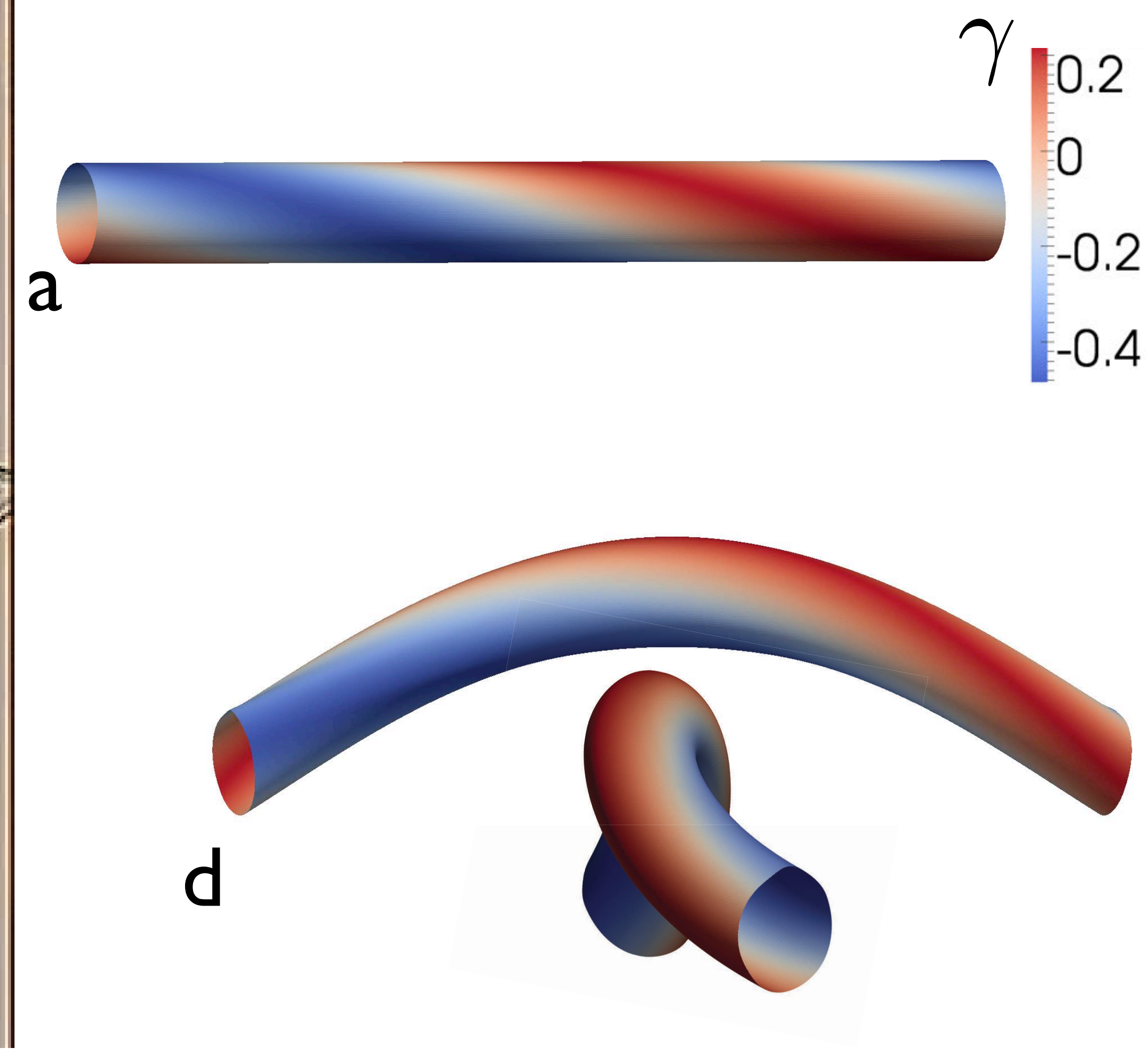
modeling the pellicle kinematics

- K=cst



modeling the pellicle kinematics

Non-axisymmetric shapes



Characterization of achievable non-axisymmetric shapes through this mechanism?

modeling the pellicle kinematics

The forward problem (find isometric embedding)

$$\begin{bmatrix} \boldsymbol{x}_{,u}\cdot\boldsymbol{x}_{,u} & \boldsymbol{x}_{,u}\cdot\boldsymbol{x}_{,v} \\ \boldsymbol{x}_{,u}\cdot\boldsymbol{x}_{,v} & \boldsymbol{x}_{,v}\cdot\boldsymbol{x}_{,v} \end{bmatrix} = \begin{bmatrix} 1 & \gamma \\ \gamma & 1+\gamma^2 \end{bmatrix}$$

may have **infinitely many or no solutions** depending on $\gamma(u,v)$

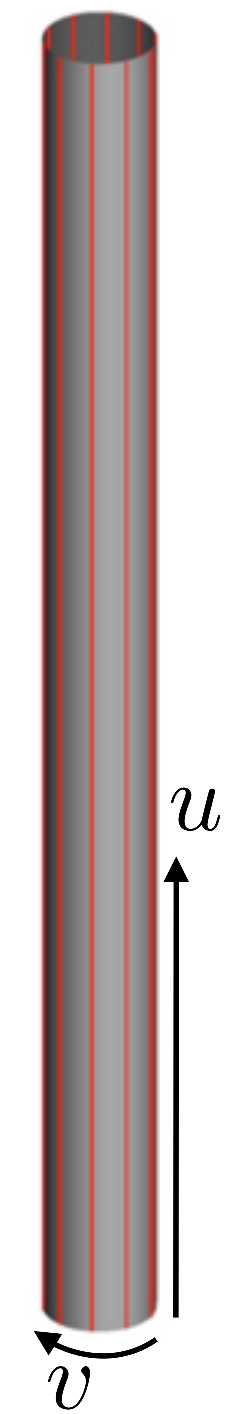
When this geometric model fails, mechanics comes to its rescue:

- bending energy minimization is a selection principle when multiple solutions *(Lewicka and Pakzad, 2011)*
- the system can stretch to approximately accommodate a non-embeddable target metric *(Efrati et al, 2009)*

$$w_{2D}(\boldsymbol{C},\boldsymbol{\mathcal{K}};\bar{\boldsymbol{C}}) = \frac{t}{2}\mathcal{A}^{IJKL}E_{IJ}E_{KL} + \frac{t^3}{24}\mathcal{A}^{IJKL}\mathcal{K}_{IJ}\mathcal{K}_{KL}$$

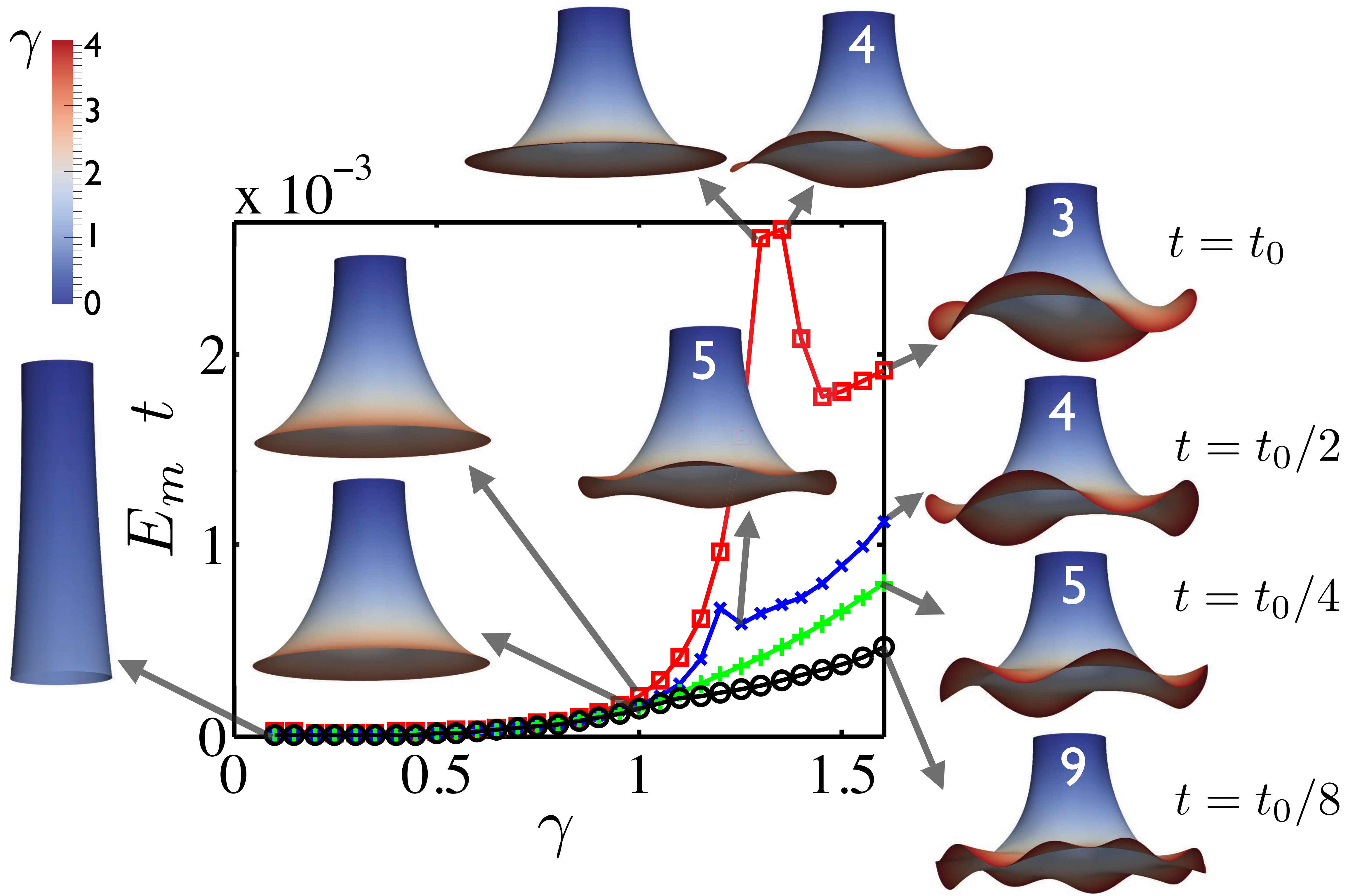
elastic energy density of a non-Euclidean shell

$$\boldsymbol{E} = 1/2(\boldsymbol{C}-\bar{\boldsymbol{C}})$$



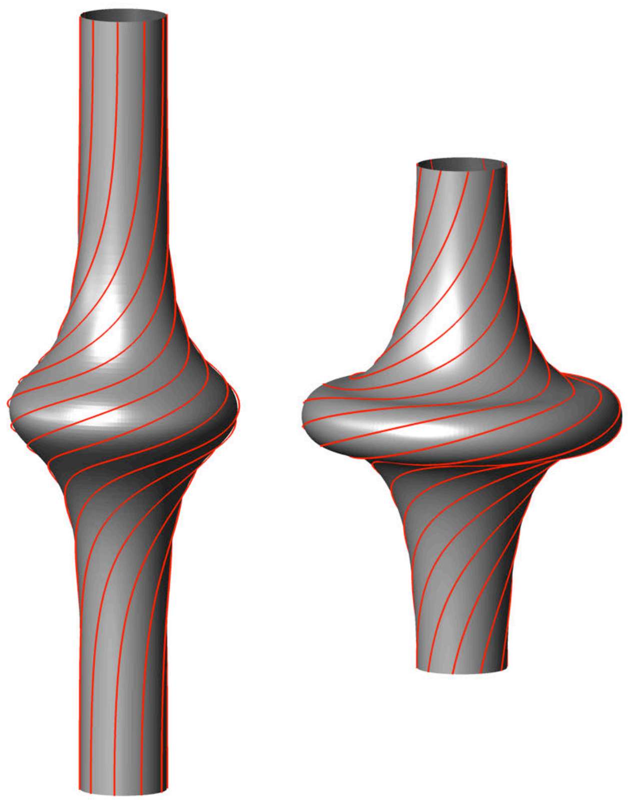
modeling the pellicle kinematics

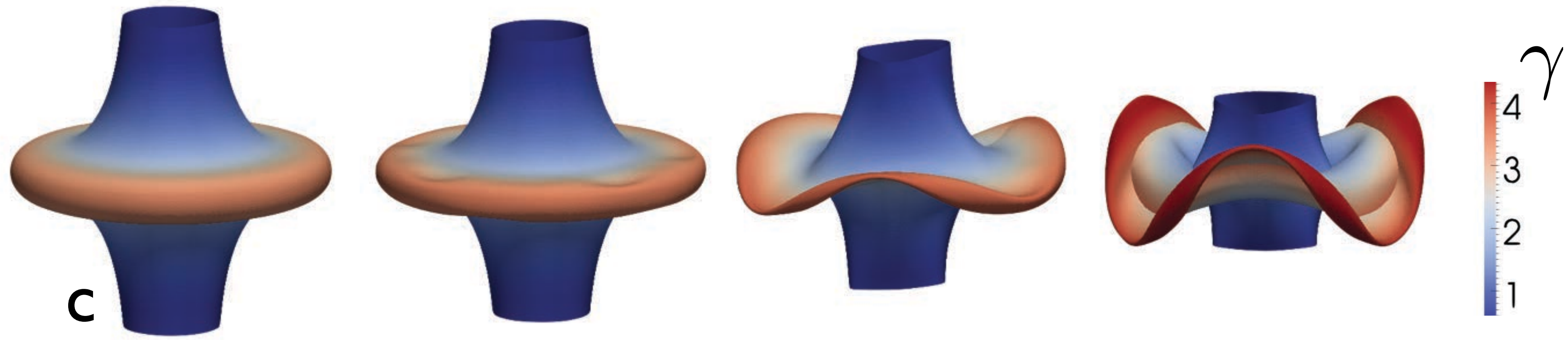
- Beyond embeddability.



modeling the pellicle kinematics

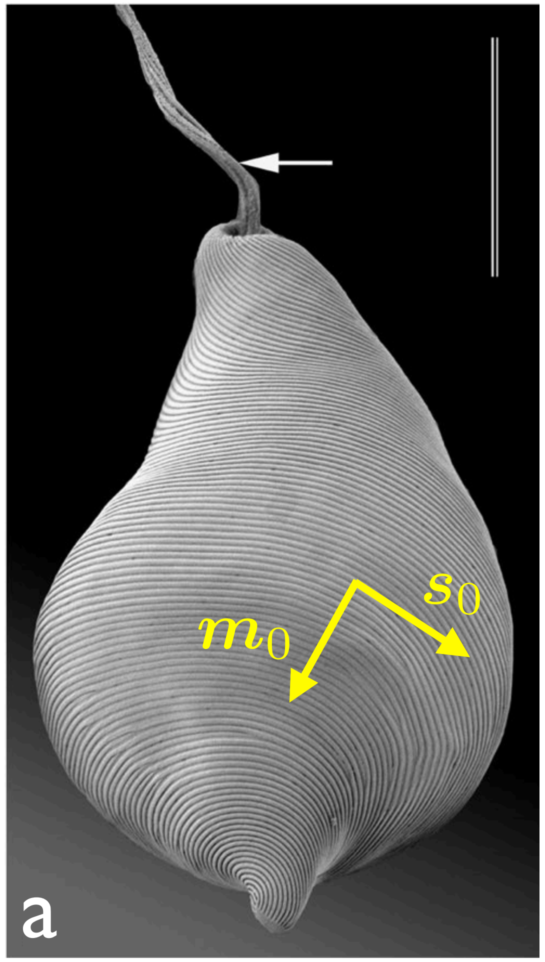
- Beyond embeddability.





back to *metaboly*

More general shapes can be obtained if γ is not uniform:



Given a reference configuration and a field of pellicle shears, **the local deformation (metric tensor)** of the surface is

$$\boldsymbol{C} = \boldsymbol{Id} + \gamma\,(\boldsymbol{s}_0 \otimes \boldsymbol{m}_0 + \boldsymbol{m}_0 \otimes \boldsymbol{s}_0) + \gamma^2 \boldsymbol{m}_0 \otimes \boldsymbol{m}_0 \qquad (1)$$

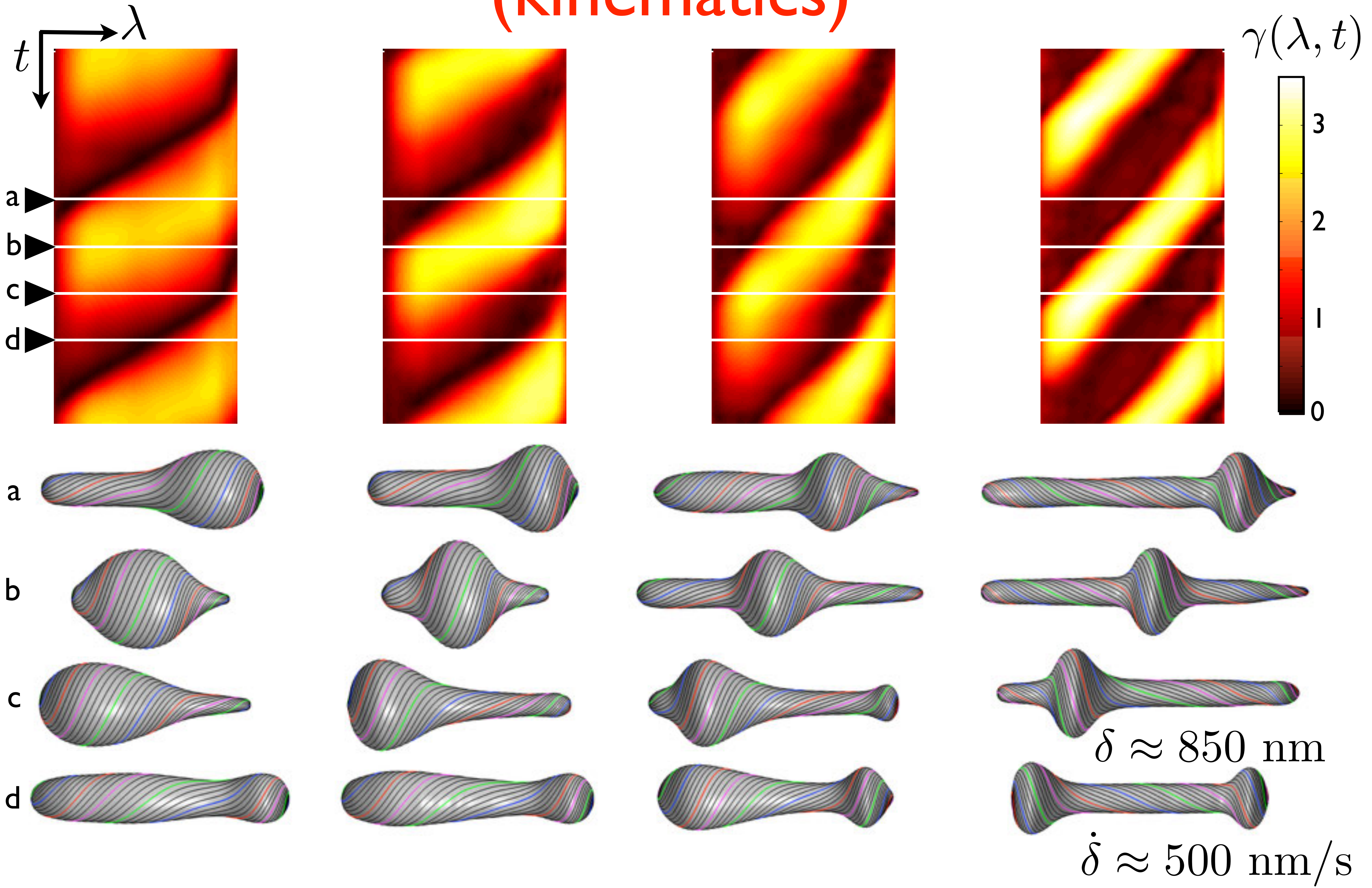
On the other hand, given a deformed configuration $\boldsymbol{x}(u,v)$ the local deformation can be written as

$$C_{IJ} = g_{IJ} = \boldsymbol{x}_{,I} \cdot \boldsymbol{x}_{,J} \qquad (2)$$

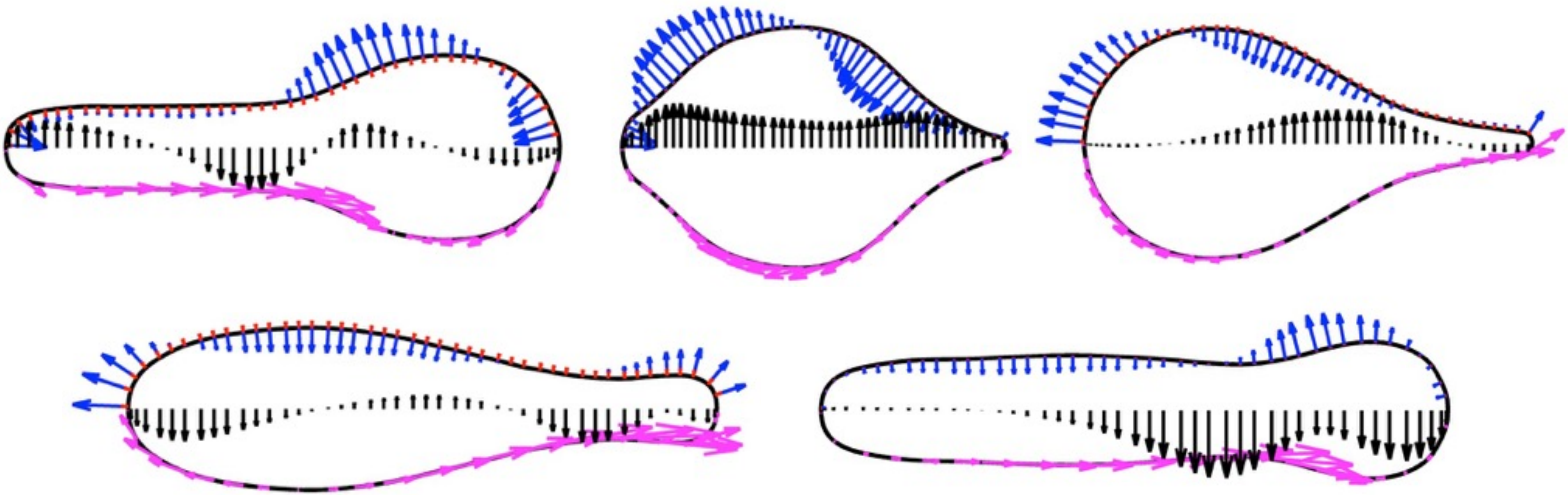
"Forward problem": given $\gamma(u,v)$, find an isometric embedding of the metric tensor in (1)—the *target metric.*

"Inverse problem": given $\boldsymbol{x}(u,v)$, find the pellicle shear $\gamma(u,v)$ such that (1) and (2) agree.

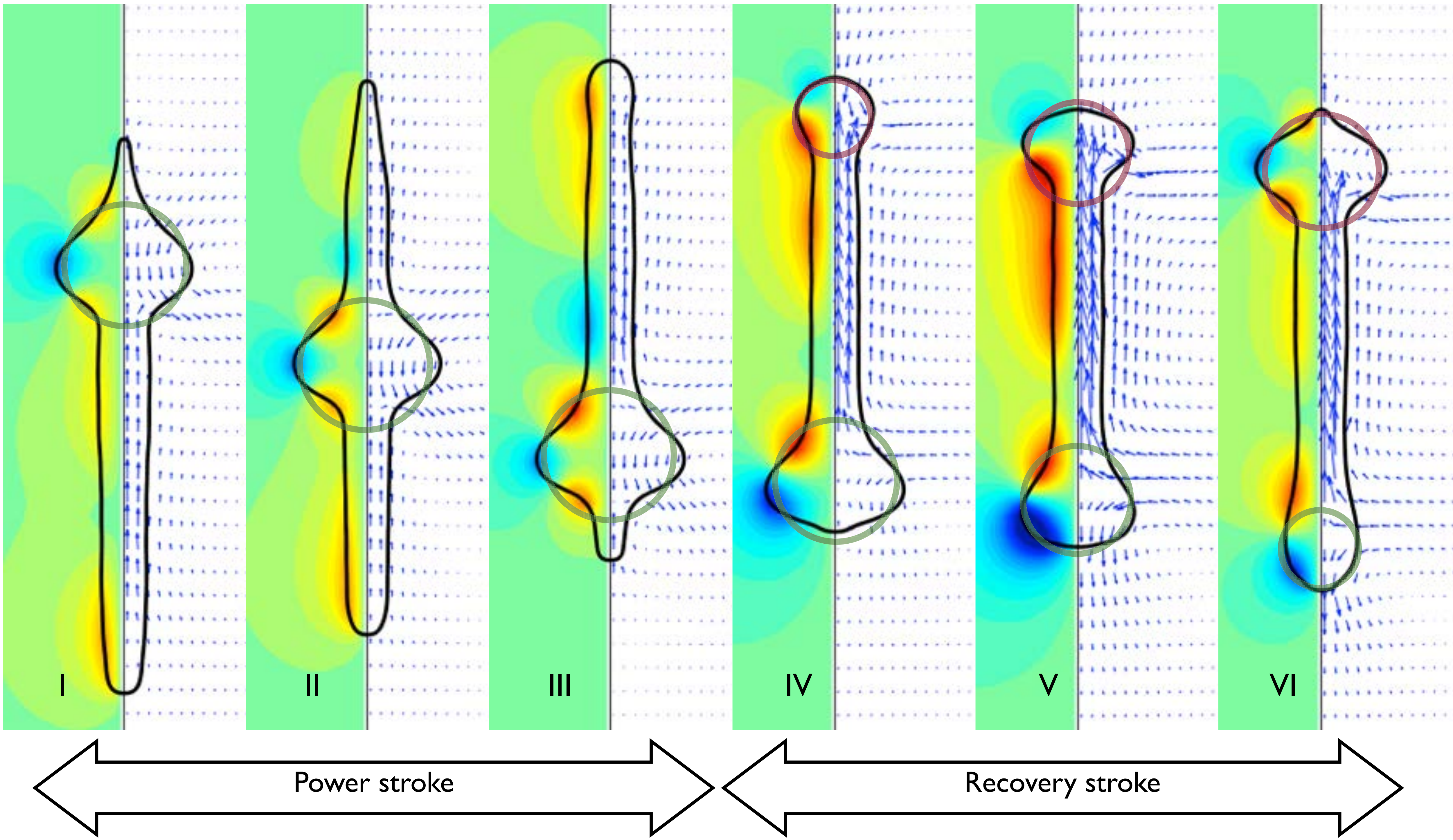
back to *metaboly*
(kinematics)



back to *metaboly*
(hydrodynamics)



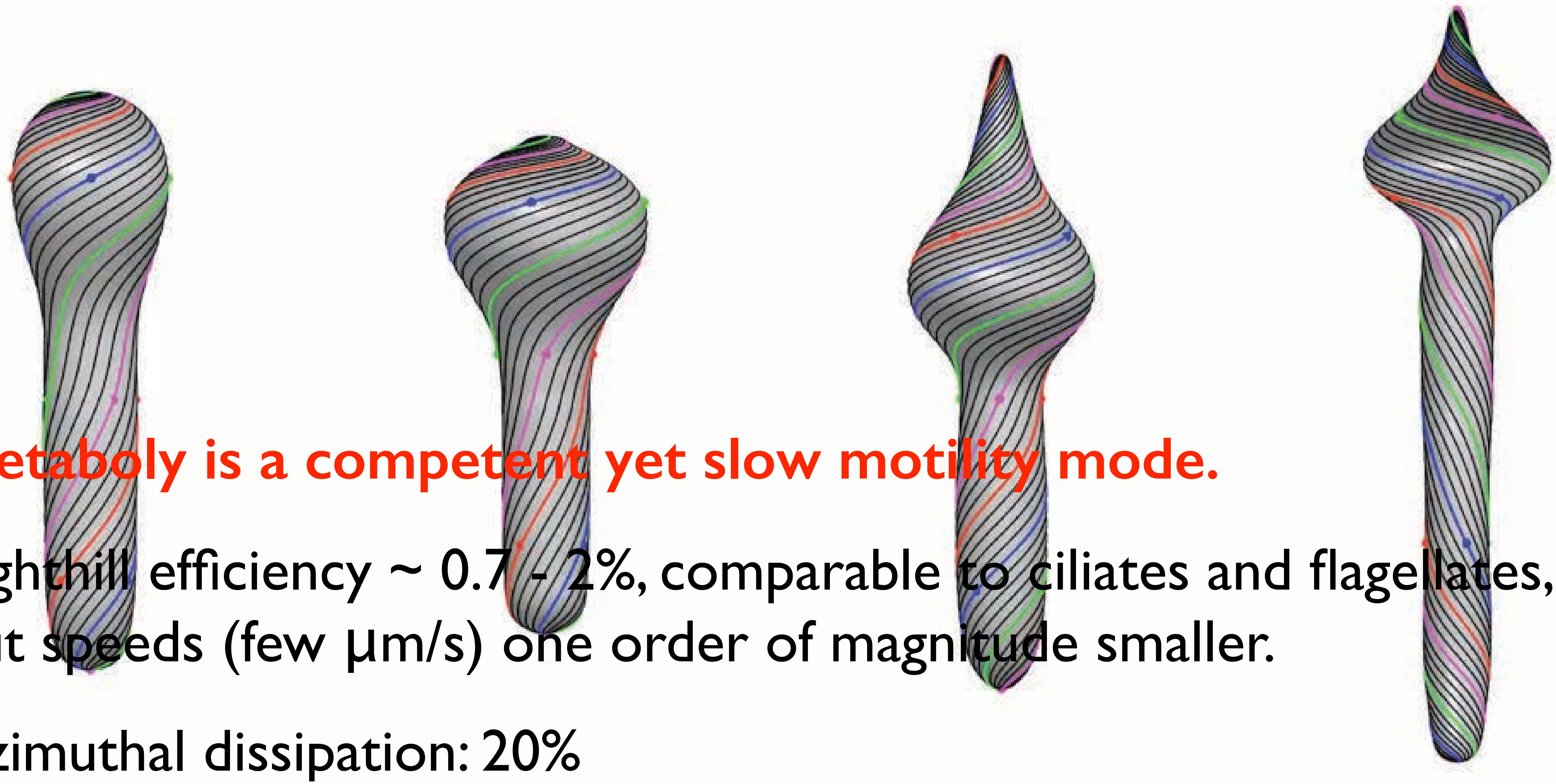
back to *metaboly*
(hydrodynamics)



propels the cell forward

moves pellicle area and fluid volume to the head of the cell

back to *metaboly*
(hydrodynamics)



Metaboly is a competent yet slow motility mode.

Lighthill efficiency ~ 0.7 - 2%, comparable to ciliates and flagellates, but speeds (few µm/s) one order of magnitude smaller.

Azimuthal dissipation: 20%

conclusions

- Precise understanding of new shape actuation principle: pellicle kinematics.
- This understanding allows us to reverse-engineer the euglenoid movement: it is a competent yet very slow mode.
- …and also provides inspiration for artificial structured interfaces: balance between flexibility and controllability.

Arroyo, Heltai, Millán DeSimone, PNAS'12
Arroyo, DeSimone, JMPS'14
Noselli, Arroyo, DeSimone, in preparation