Computational Models for the Growth of Closed Bacterial Cell Envelopes

Paul Schulze

2023-01-19

Outline

- Introduction
- Spring-based model
  - Idea behind the model
  - Results
- Finite-element-based model
  - Idea behind the model
  - Results
- Summary
- Outlook

- **Introduction**
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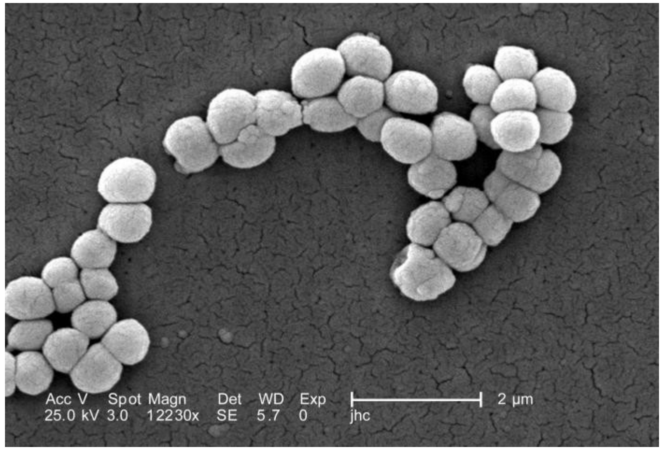
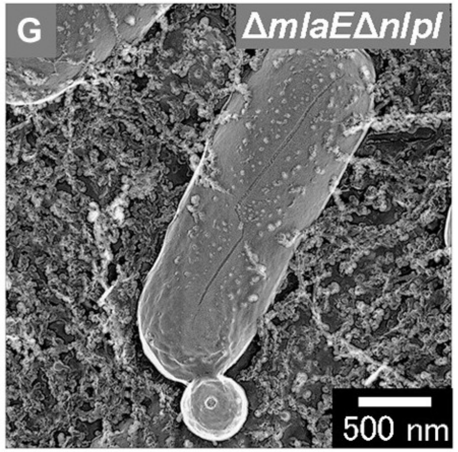
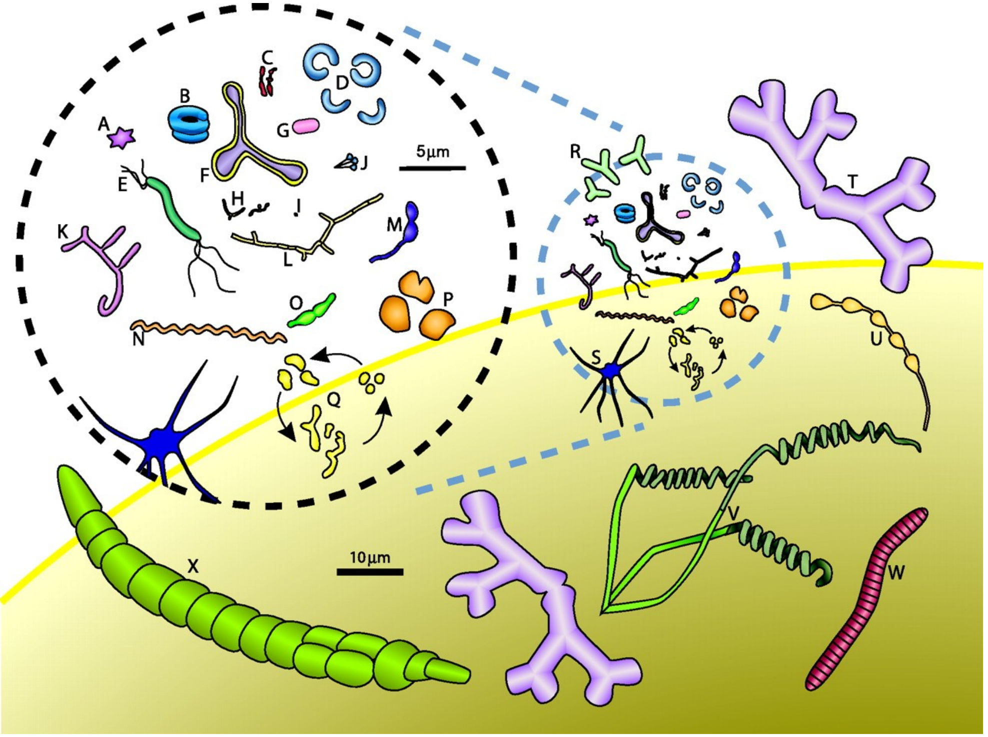
Shapes of bacteria



Carr, J. H. (2007) Public Health Image Library (PHIL), CDC



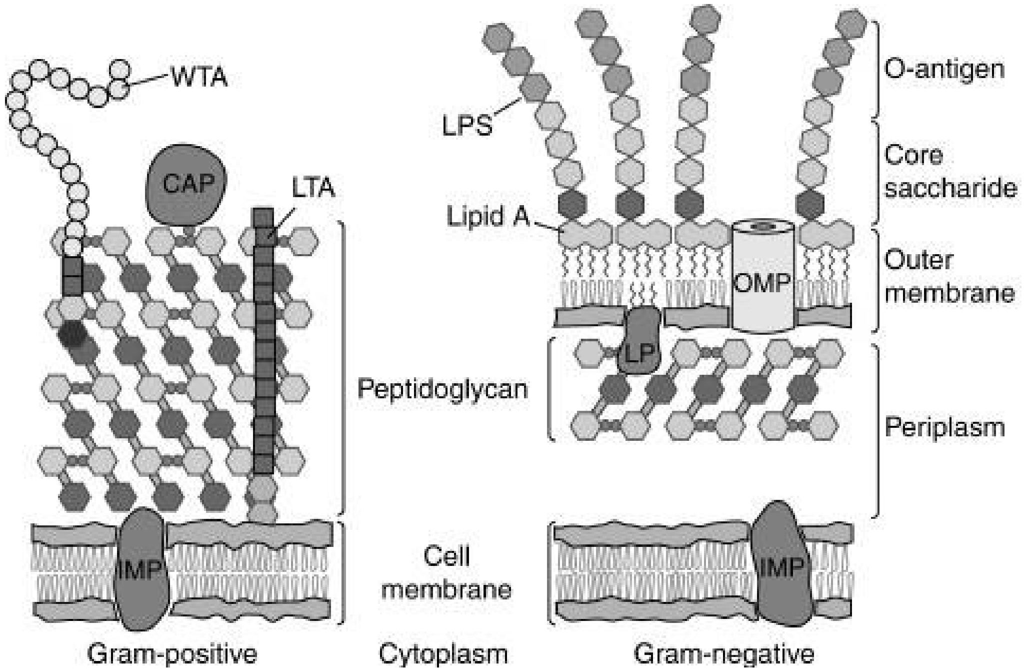
Ojima, Y. (2021) Microbial Physiology and Metabolism



Young, K. D. (2006) Microbiology and molecular biology reviews

The cell wall determines the shape

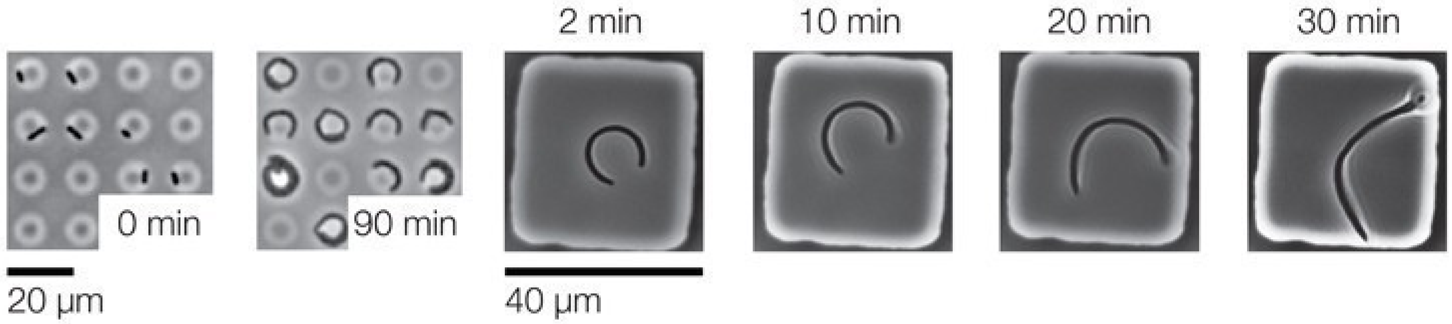
- Composed of Peptodoglycan
- Protects against *osmotic pressure*
- Two classes of bacteria
  - Gram-positive: Thick cell wall
  - Gram-negative: Thin cell wall



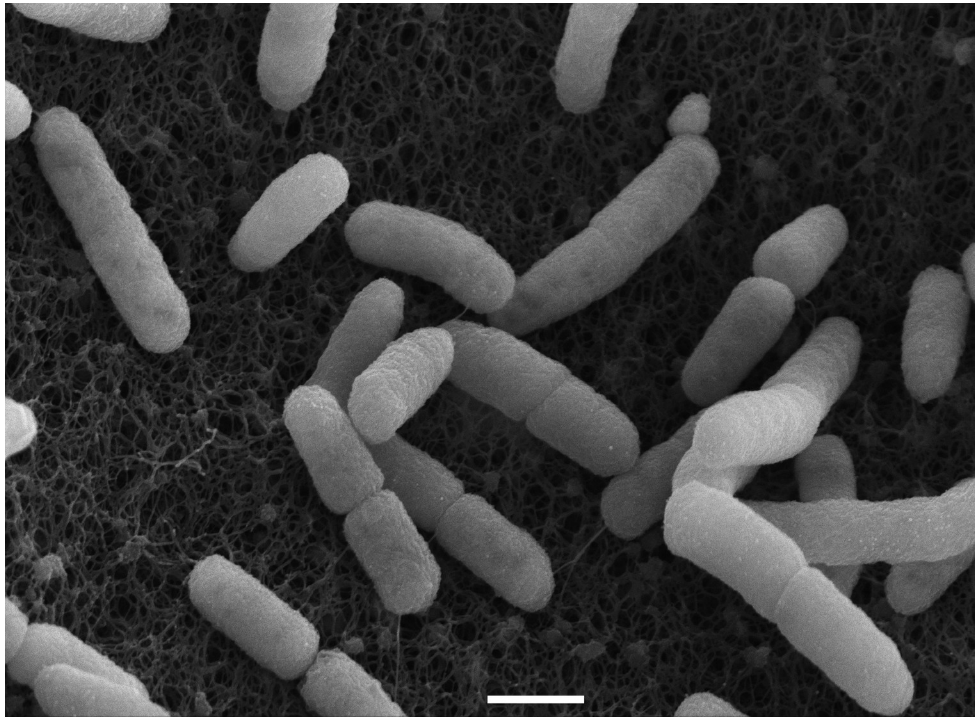
Silhavy, T. J. (2010) in Cold Spring Harbor perspectives in biology

Shape preservation in bacteria

- Shape is consistent through generations
- Shape is recovered after disturbance
- Shape changes in response to the environment

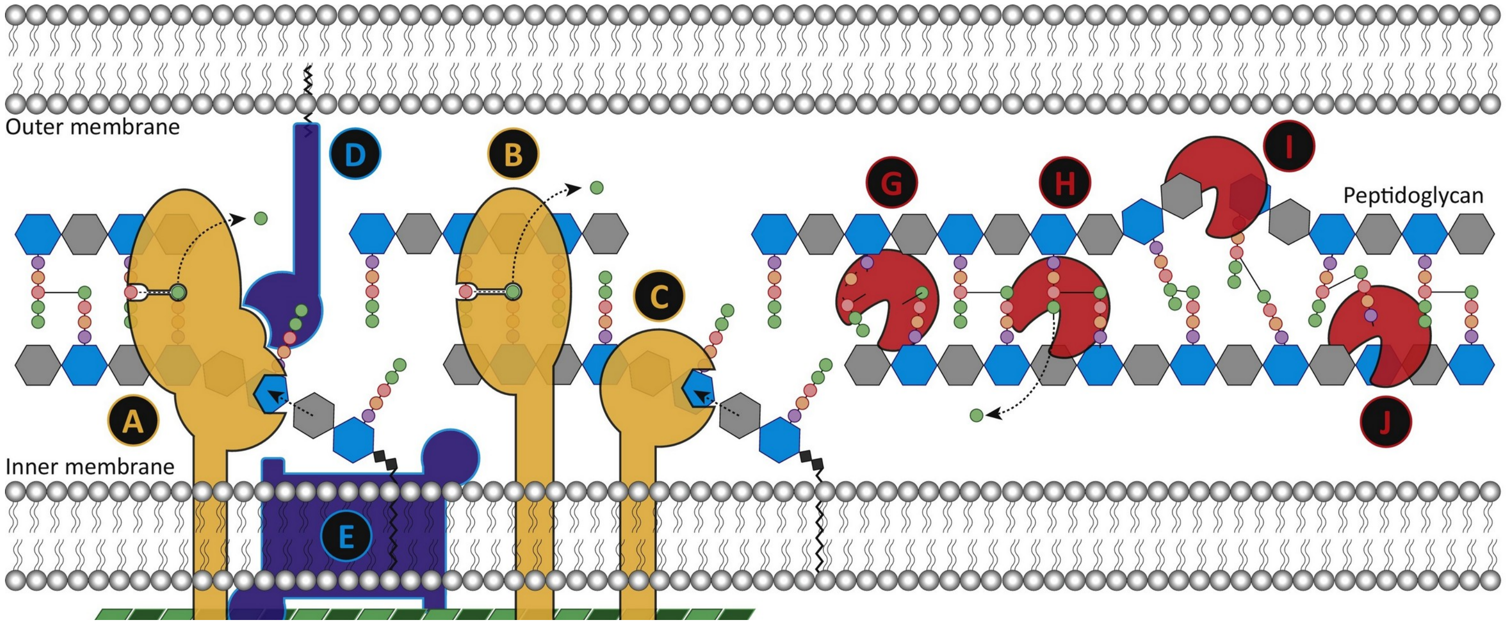


Reproduced from: Felix Wong et al. (2017) Nature microbiology



Gudrun Holland,Michael Laue/RKI

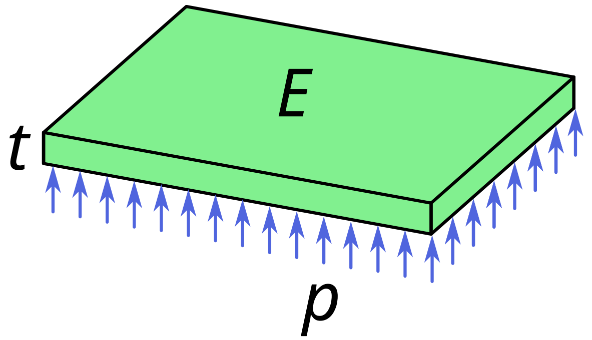
Peptidoglycan remodelling

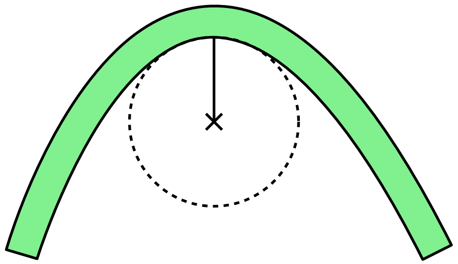


- PG synthases assemble the PG network
- PG hydrolases modify existing PG
- Guided by *mechanical / geometrical* cues?

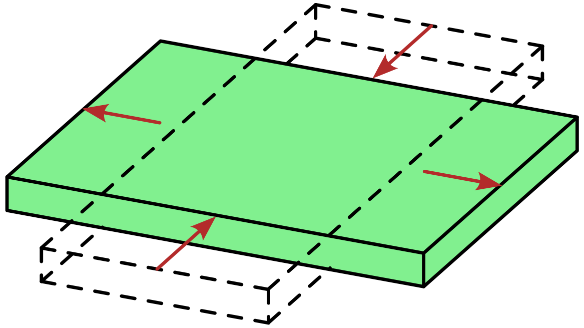
Growth model for the bacterial shell

- Mechanical properties of the cell wall
- Turgor pressure
- Growth rates are based on local cues





Curvature



Strain

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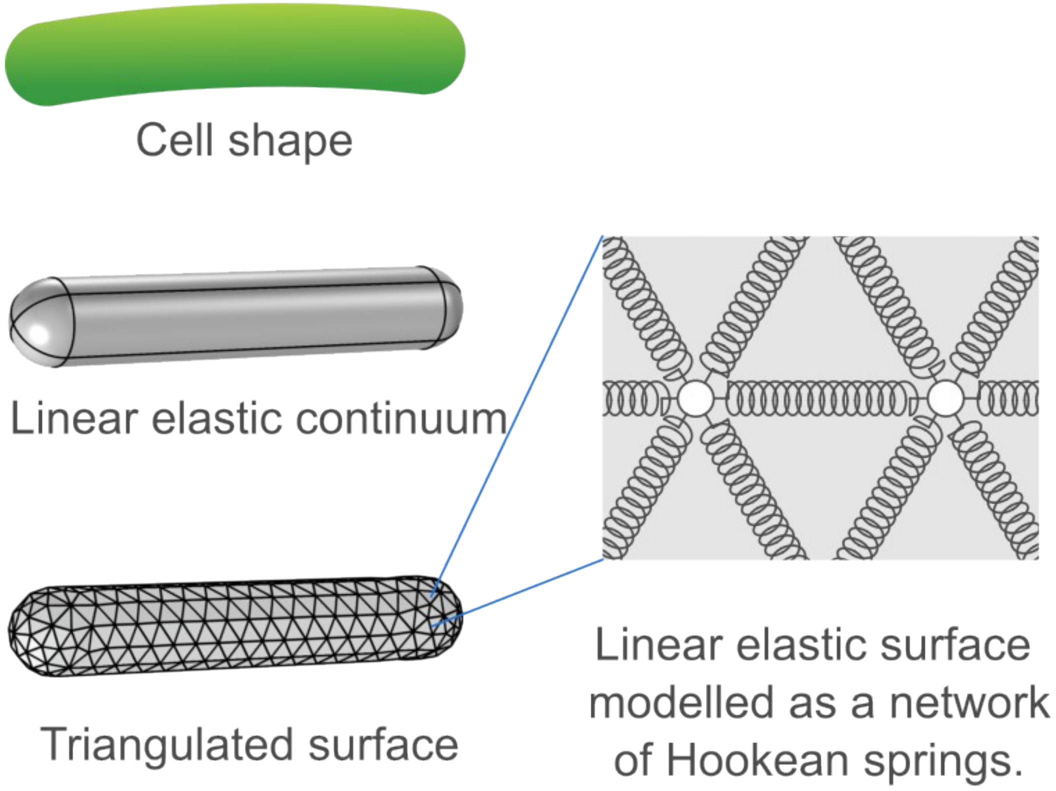
Spring-based model of the shell

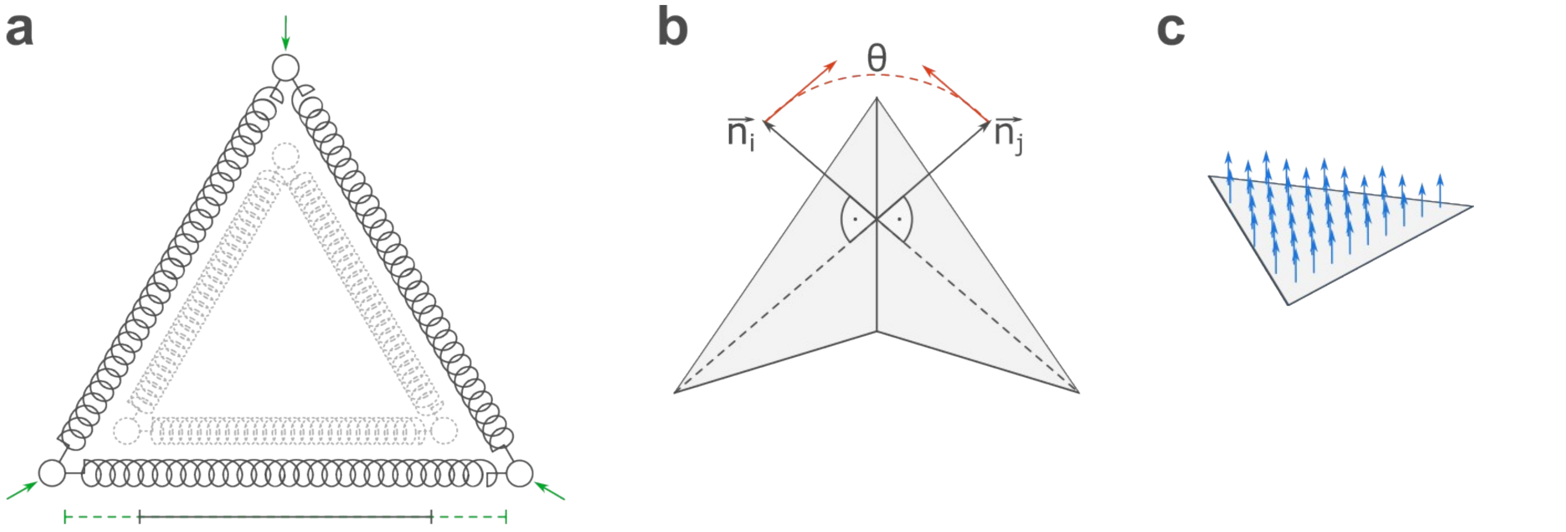
- Linear elastic continuum
  - Young's modulus E
  - Thickness t
- Spring network
  - Spring stiffness k_s
  - Bending stiffness k_b

- Mapping:

$$E, t \rightarrow k_s, k_b$$



Energy function



Spring Energy

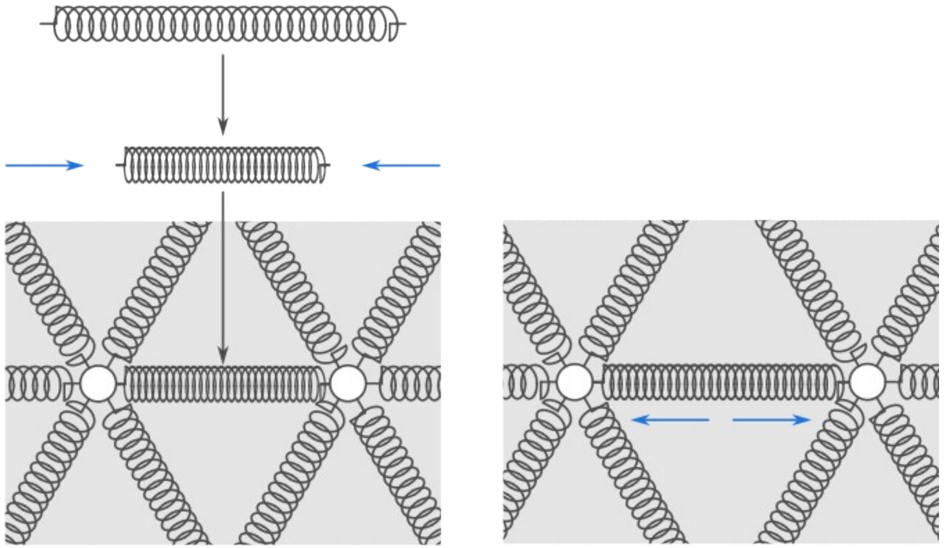
Bending Energy

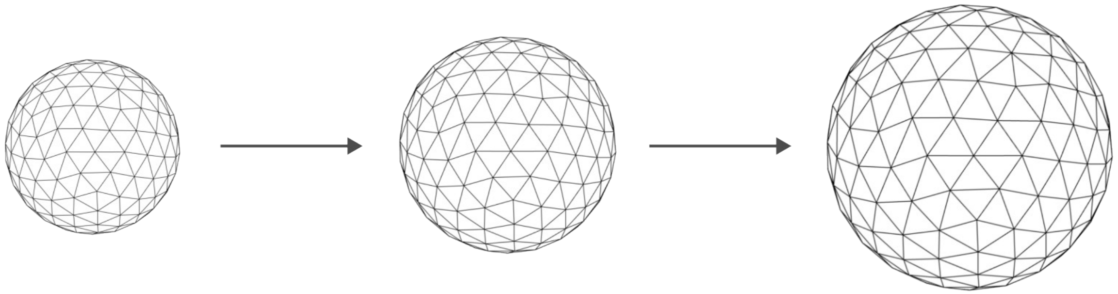
Pressure Energy

$$E = \sum_{e}^{edges} \frac{k_s}{2} (l_e - l_{0,e})^2 + \sum_{\{i,j\}(adj.)}^{triangles} k_b (1 - \vec{n}_i \vec{n}_j) - pV$$

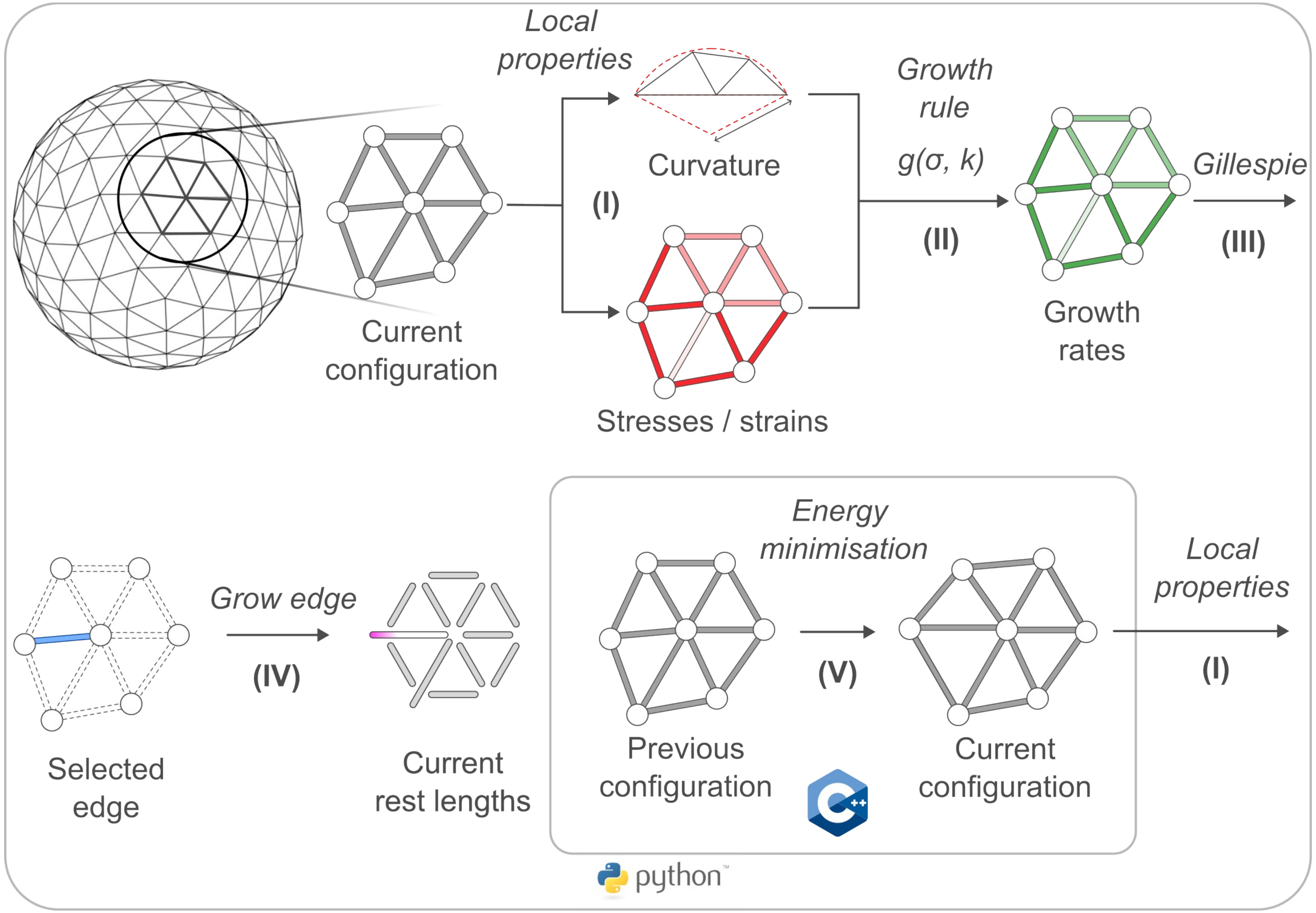
Iterative growth

- Increasing rest lengths $l_{e,0}$
- Mesh topology is consistent between growth steps





Simulation flowchart



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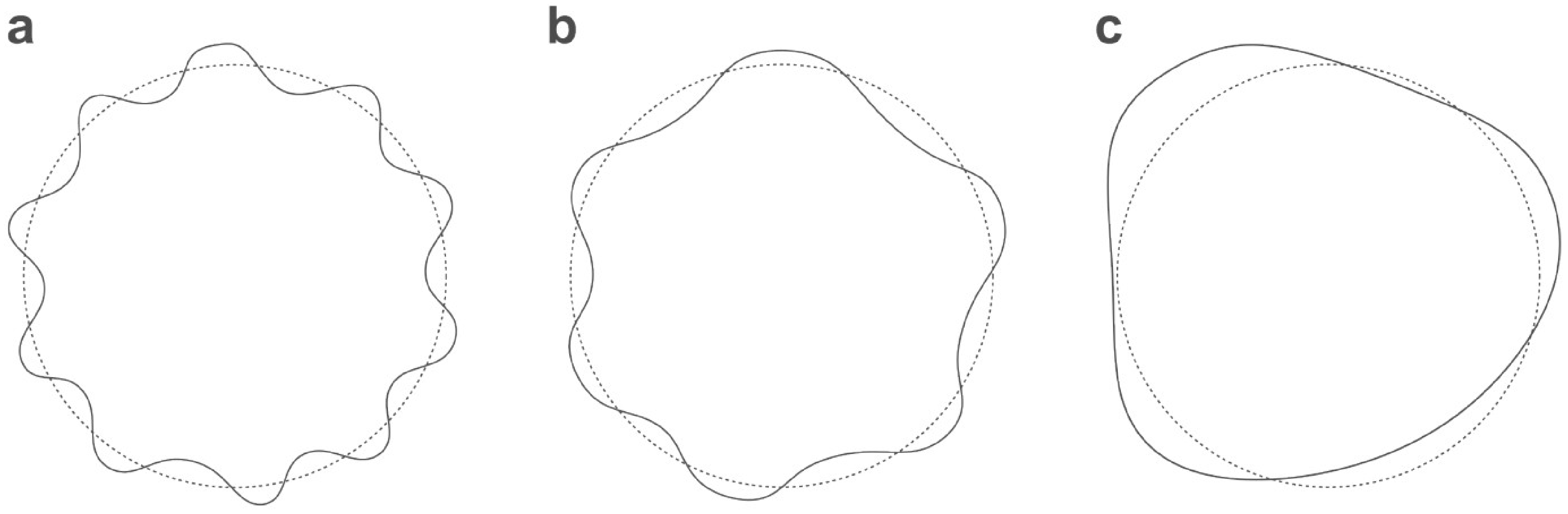
Observables



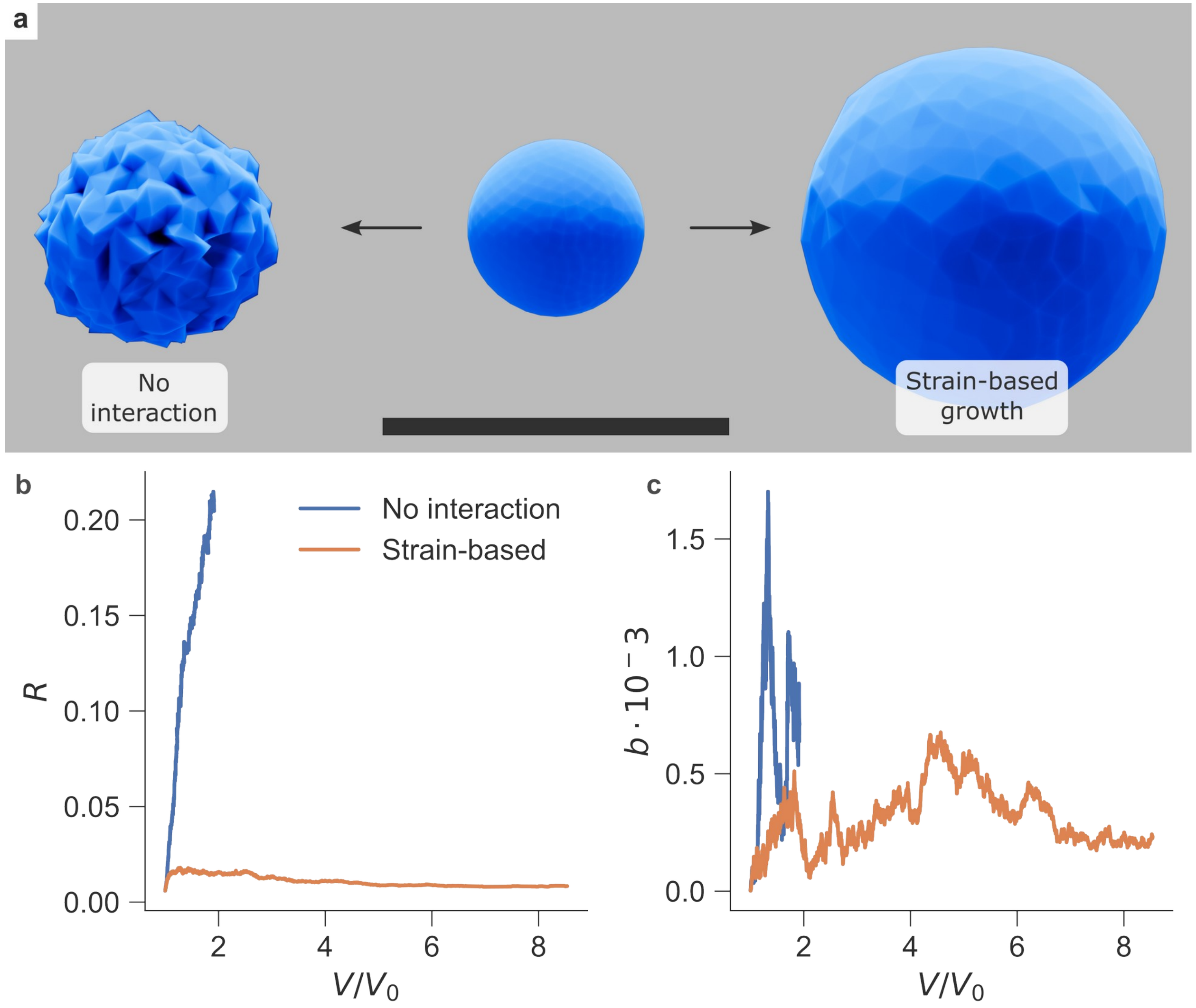
Roughness

Asphericity

Random vs. strain-based growth

Strain-based growth rates:

$$\varepsilon_e = (l_e - l_{e,0})/l_{e,0}$$
$$\lambda_e = -\lambda_0 + \lambda_1 \varepsilon_e$$



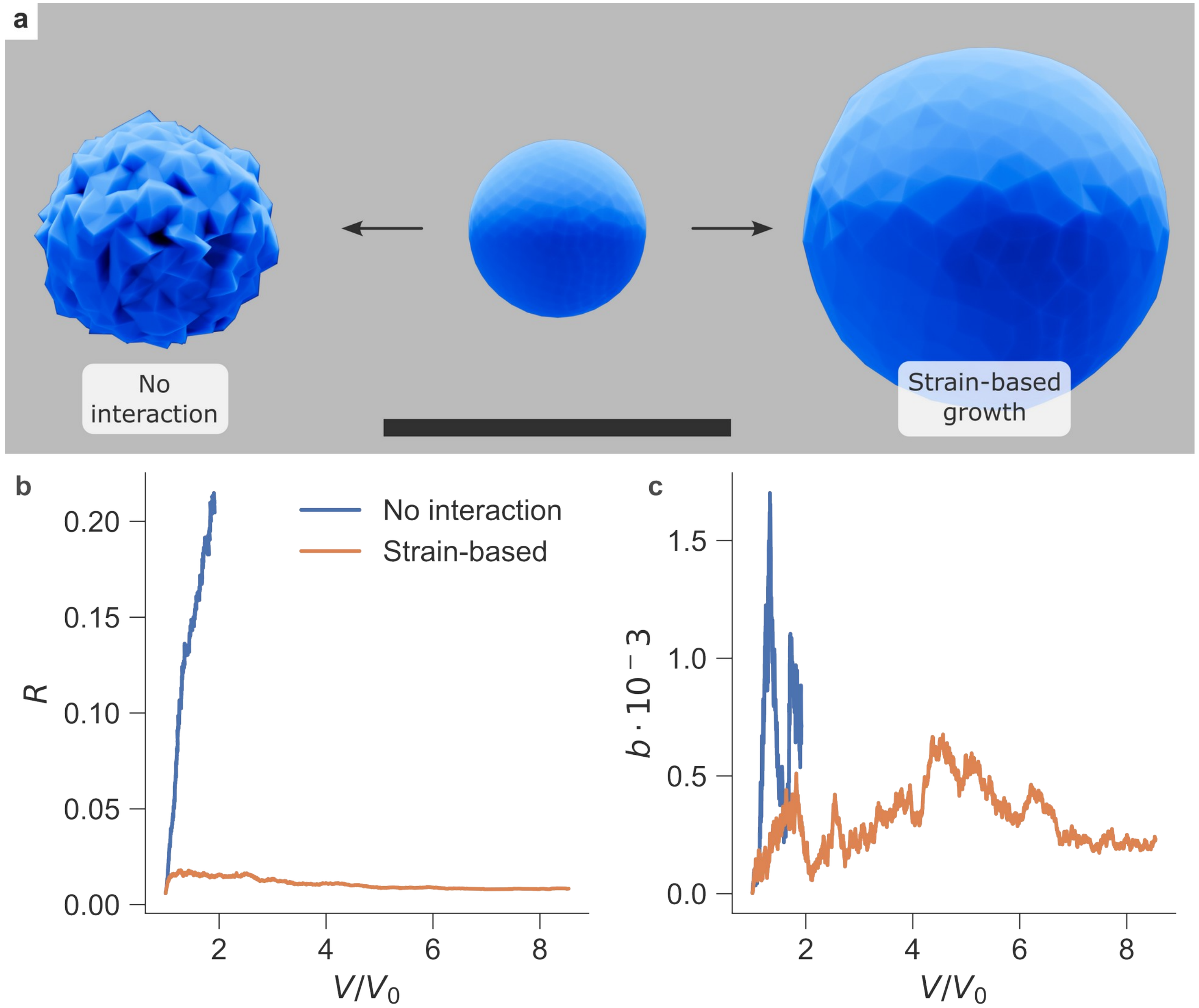
Random vs. strain-based growth

Strain-based growth rates:

$$\varepsilon_e = (l_e - l_{e,0})/l_{e,0}$$
$$\lambda_e = -\lambda_0 + \lambda_1 \varepsilon_e$$

Random
→ Spherical shape
→ Surface roughness

Strain-based
→ Spherical shape
→ Smooth surface



Random vs. strain-based growth

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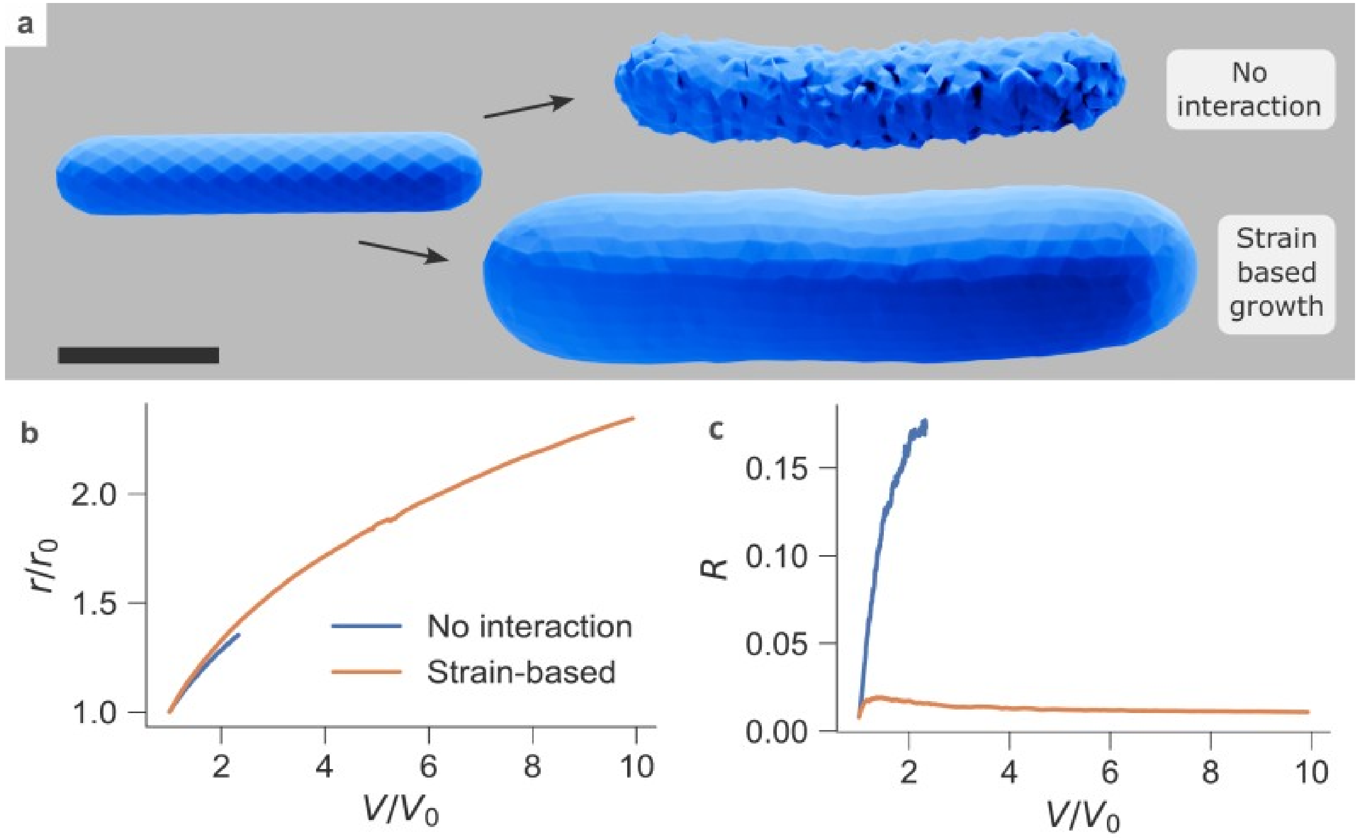


Random vs. strain-based growth

Strain-based growth rates:

$$\lambda_e = -\lambda_0 + \lambda_1 \varepsilon_e$$

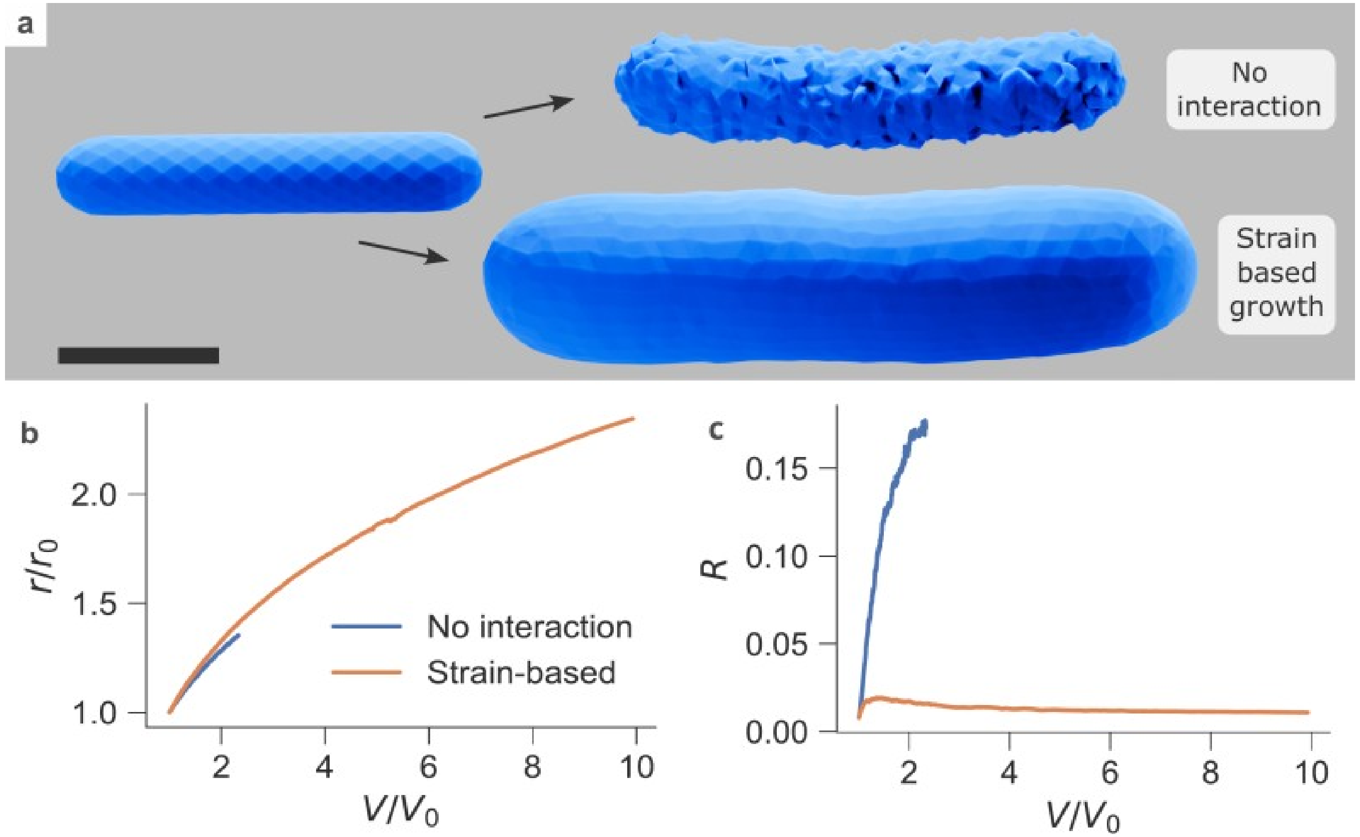
Random growth

→ Cylindrical shape
→ Surface roughness

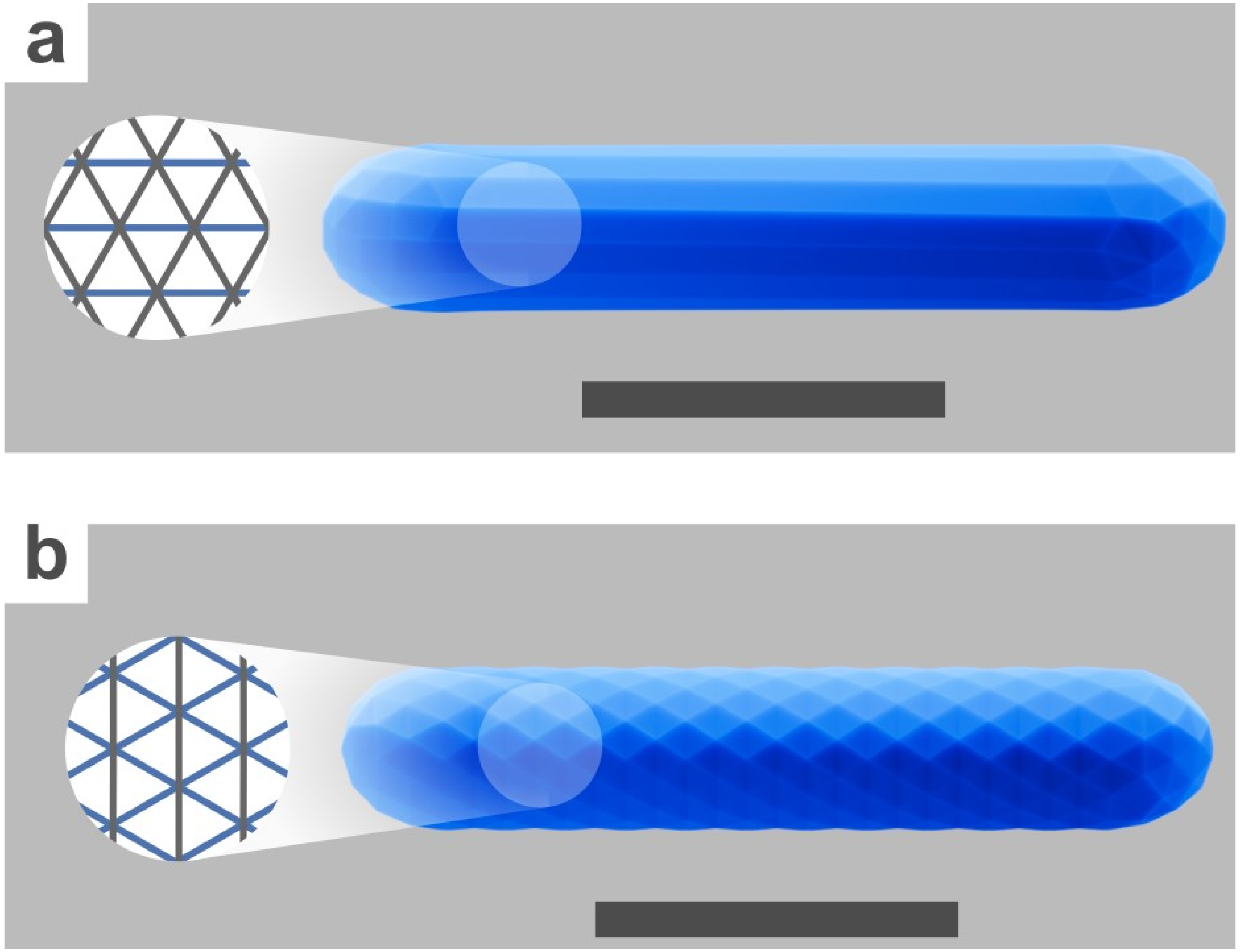
Strain-based growth

→ Cylindrical shape
→ Smooth surface

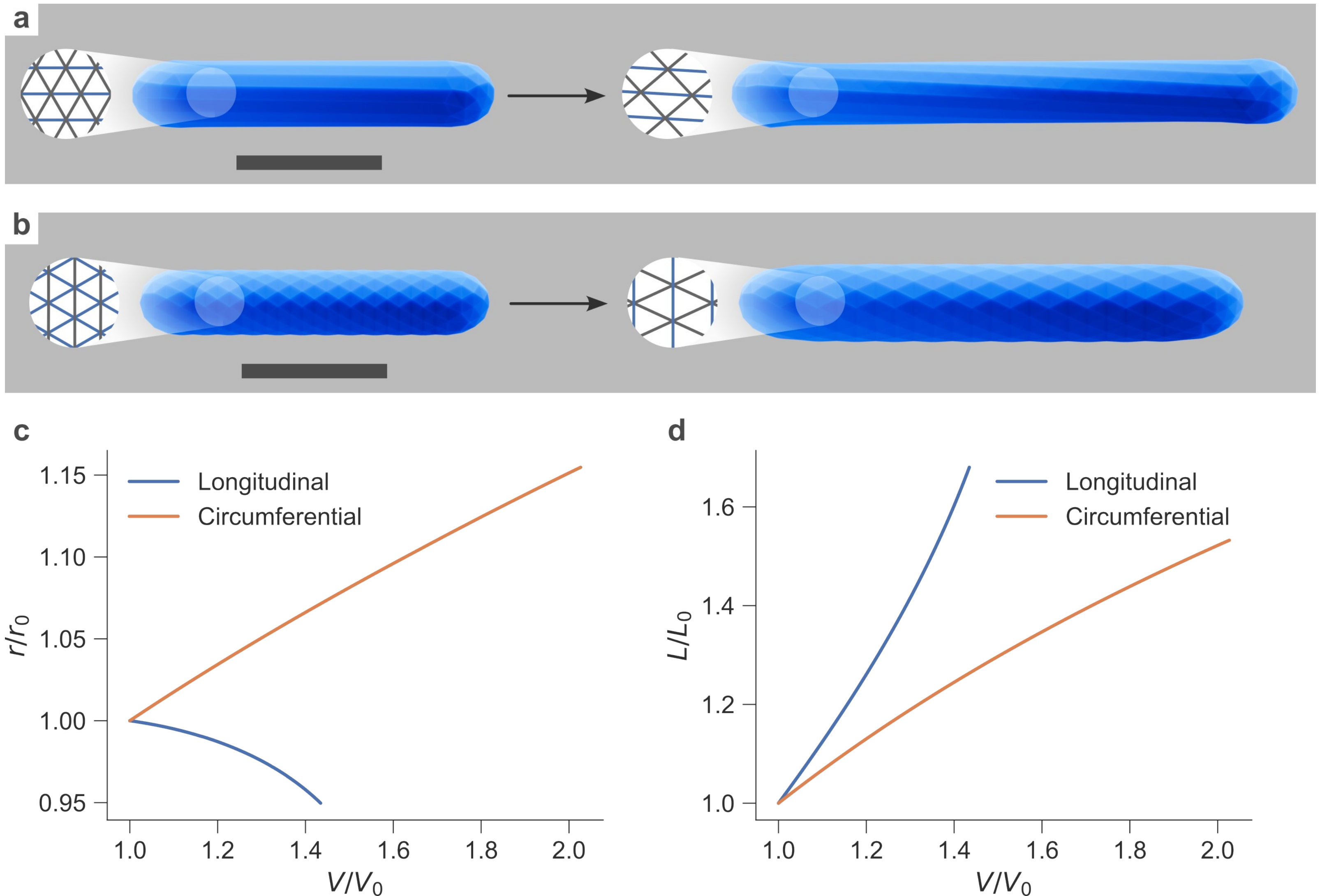
$\Longrightarrow$ Radius is <u>not conserved</u>



Directed growth: Mesh alignment



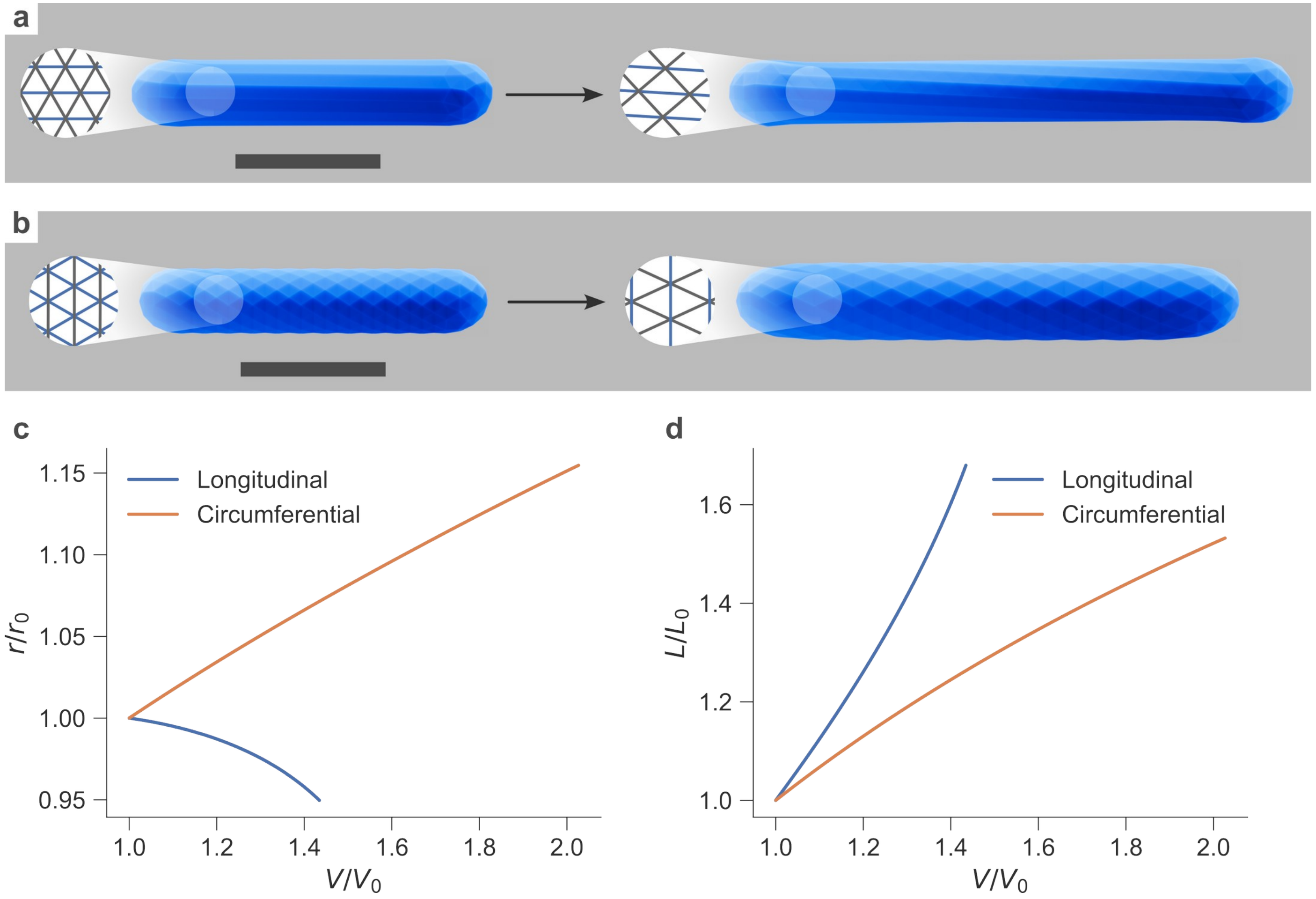
Directed growth: Mesh alignment



Spring-based model: Limitations

- Dependence on *mesh alignment*
- Acute angles in triangles → Not linear elastic
- Hyperelasticity

→ Alternative model



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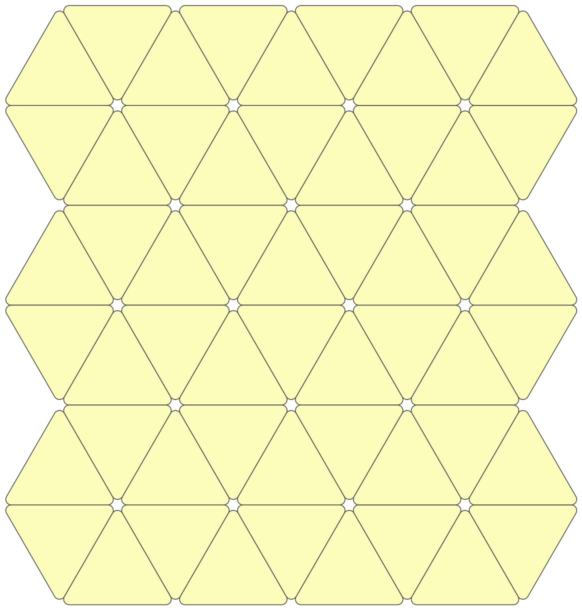
Finite element method

- Method to solve partial differential equations (PDEs)
- Solve for deformations of complex geometries under outside forces
- Surface is divided into elements
- Solution is evaluated at nodes
- Interpolated for a full solution



Finite element method

Strain for triangular element:

$$\vec{\varepsilon} = [B]\vec{u}_{\text{element}} = \begin{bmatrix} \varepsilon_{11} \\ \varepsilon_{22} \\ 2\varepsilon_{12} \end{bmatrix} = \begin{bmatrix} \frac{\partial N_a}{\partial x_1} & 0 & \frac{\partial N_b}{\partial x_1} & 0 & \frac{\partial N_c}{\partial x_1} & 0 \\ 0 & \frac{\partial N_a}{\partial x_2} & 0 & \frac{\partial N_b}{\partial x_2} & 0 & \frac{\partial N_c}{\partial x_2} \\ \frac{\partial N_a}{\partial x_1} & \frac{\partial N_a}{\partial x_2} & \frac{\partial N_b}{\partial x_1} & \frac{\partial N_b}{\partial x_2} & \frac{\partial N_c}{\partial x_1} & \frac{\partial N_c}{\partial x_2} \end{bmatrix} \begin{bmatrix} u_1^{(a)} \\ u_2^{(a)} \\ u_1^{(b)} \\ u_2^{(b)} \\ u_1^{(c)} \\ u_2^{(c)} \end{bmatrix}$$

Finite element method

Strain for triangular element:

$$\vec{\varepsilon} = [B]\vec{u}_{\text{element}} = \begin{bmatrix} \varepsilon_{11} \\ \varepsilon_{22} \\ 2\varepsilon_{12} \end{bmatrix} = \begin{bmatrix} \frac{\partial N_a}{\partial x_1} & 0 & \frac{\partial N_b}{\partial x_1} & 0 & \frac{\partial N_c}{\partial x_1} & 0 \\ 0 & \frac{\partial N_a}{\partial x_2} & 0 & \frac{\partial N_b}{\partial x_2} & 0 & \frac{\partial N_c}{\partial x_2} \\ \frac{\partial N_a}{\partial x_1} & \frac{\partial N_a}{\partial x_2} & \frac{\partial N_b}{\partial x_1} & \frac{\partial N_b}{\partial x_2} & \frac{\partial N_c}{\partial x_1} & \frac{\partial N_c}{\partial x_2} \end{bmatrix} \begin{bmatrix} u_1^{(a)} \\ u_2^{(a)} \\ u_1^{(b)} \\ u_2^{(b)} \\ u_1^{(c)} \\ u_2^{(c)} \end{bmatrix}$$

Stress-strain relation:

$$\begin{bmatrix} \sigma_{11} \\ \sigma_{22} \\ \sigma_{12} \end{bmatrix} = [D] \begin{bmatrix} \varepsilon_{11} \\ \varepsilon_{22} \\ \varepsilon_{12} \end{bmatrix} = \frac{E}{(1-\nu)^2} \begin{bmatrix} 1 & \nu & 0 \\ \nu & 1 & 0 \\ 0 & 0 & (1-\nu)/2 \end{bmatrix} \begin{bmatrix} \varepsilon_{11} \\ \varepsilon_{22} \\ \varepsilon_{12} \end{bmatrix}$$

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Strain energy:

$$U = \frac{1}{2}\vec{\varepsilon}^{\mathbf{T}}\vec{\sigma} = \frac{1}{2}\vec{\varepsilon}^{\mathbf{T}}[D]\vec{\varepsilon}.$$

Finite element method

$$\vec{\varepsilon} = [B]\vec{u}_{\text{element}} \qquad U = \frac{1}{2}\vec{\varepsilon}^{\mathbf{T}}\vec{\sigma} = \frac{1}{2}\vec{\varepsilon}^{\mathbf{T}}[D]\vec{\varepsilon}.$$

Finite element method

$$\vec{\varepsilon} = [B]\vec{u}_{\text{element}} \qquad U = \frac{1}{2}\vec{\varepsilon}^{\mathbf{T}}\vec{\sigma} = \frac{1}{2}\vec{\varepsilon}^{\mathbf{T}}[D]\vec{\varepsilon}.$$

Strain energy for element:

$$W_{\text{element}} = \frac{1}{2}\vec{u}_{\text{element}}^{\mathbf{T}}(A_{\text{element}}[B]^{\mathbf{T}}[D][B])\vec{u}_{\text{element}}$$

Finite element method

$$\vec{\varepsilon} = [B]\vec{u}_{\text{element}} \qquad U = \frac{1}{2}\vec{\varepsilon}^{\mathbf{T}}\vec{\sigma} = \frac{1}{2}\vec{\varepsilon}^{\mathbf{T}}[D]\vec{\varepsilon}.$$

Strain energy for element:

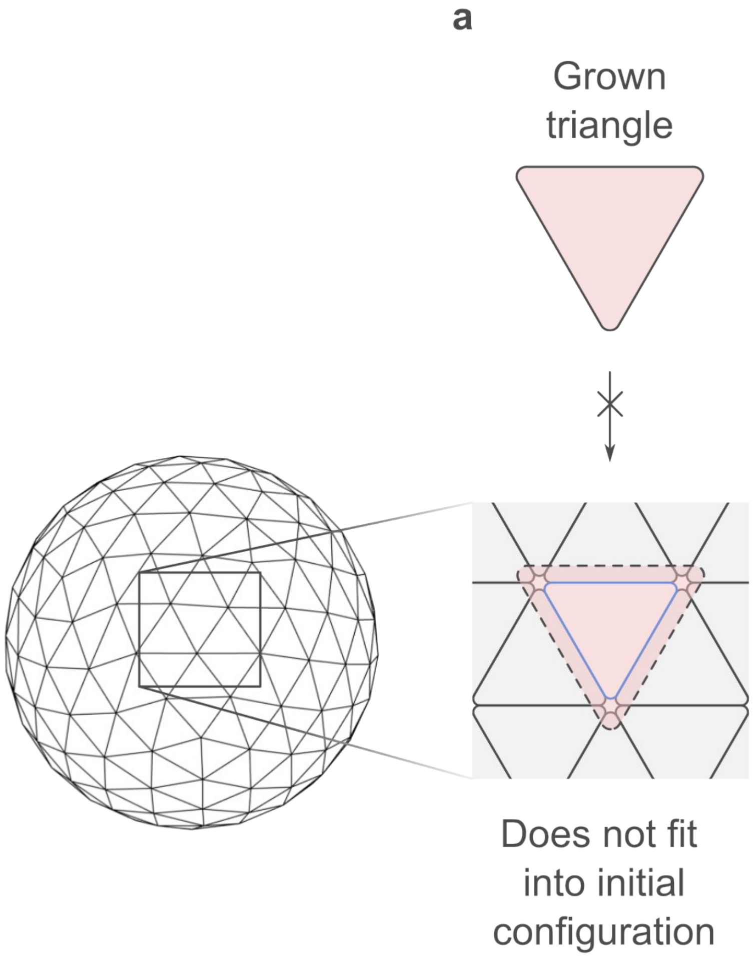
$$W_{\text{element}} = \frac{1}{2}\vec{u}_{\text{element}}^{\mathbf{T}}\left(A_{\text{element}}[B]^{\mathbf{T}}[D][B]\right)\vec{u}_{\text{element}}$$

Total strain energy:

$$W = \sum_{\text{elements}} W_{\text{element}} = \frac{1}{2}\sum_{\text{elements}} \vec{u}_{\text{element}}^{\mathbf{T}} K_{\text{element}}\vec{u}_{\text{element}}$$

Minimize *W* with respect to *u* → Deformations

Finite-element-based Model



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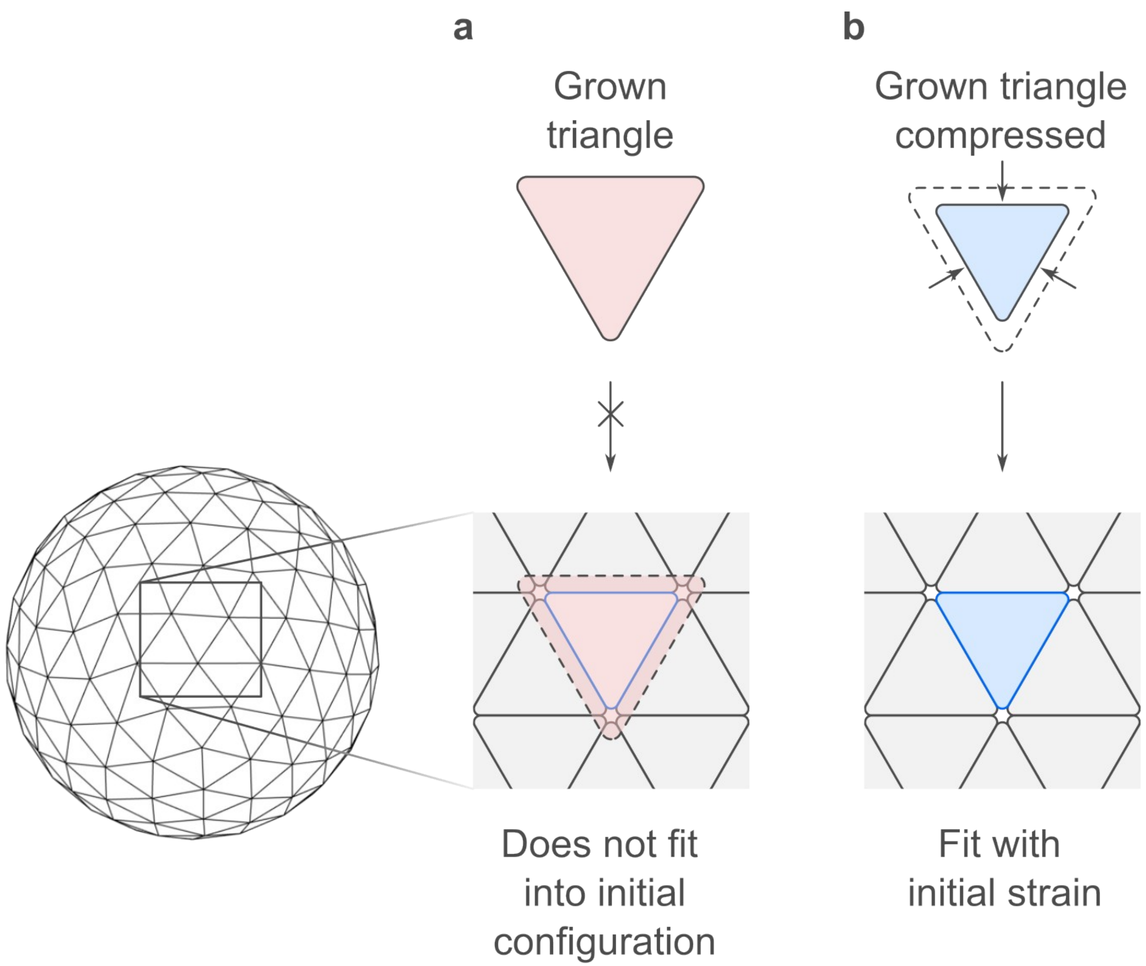

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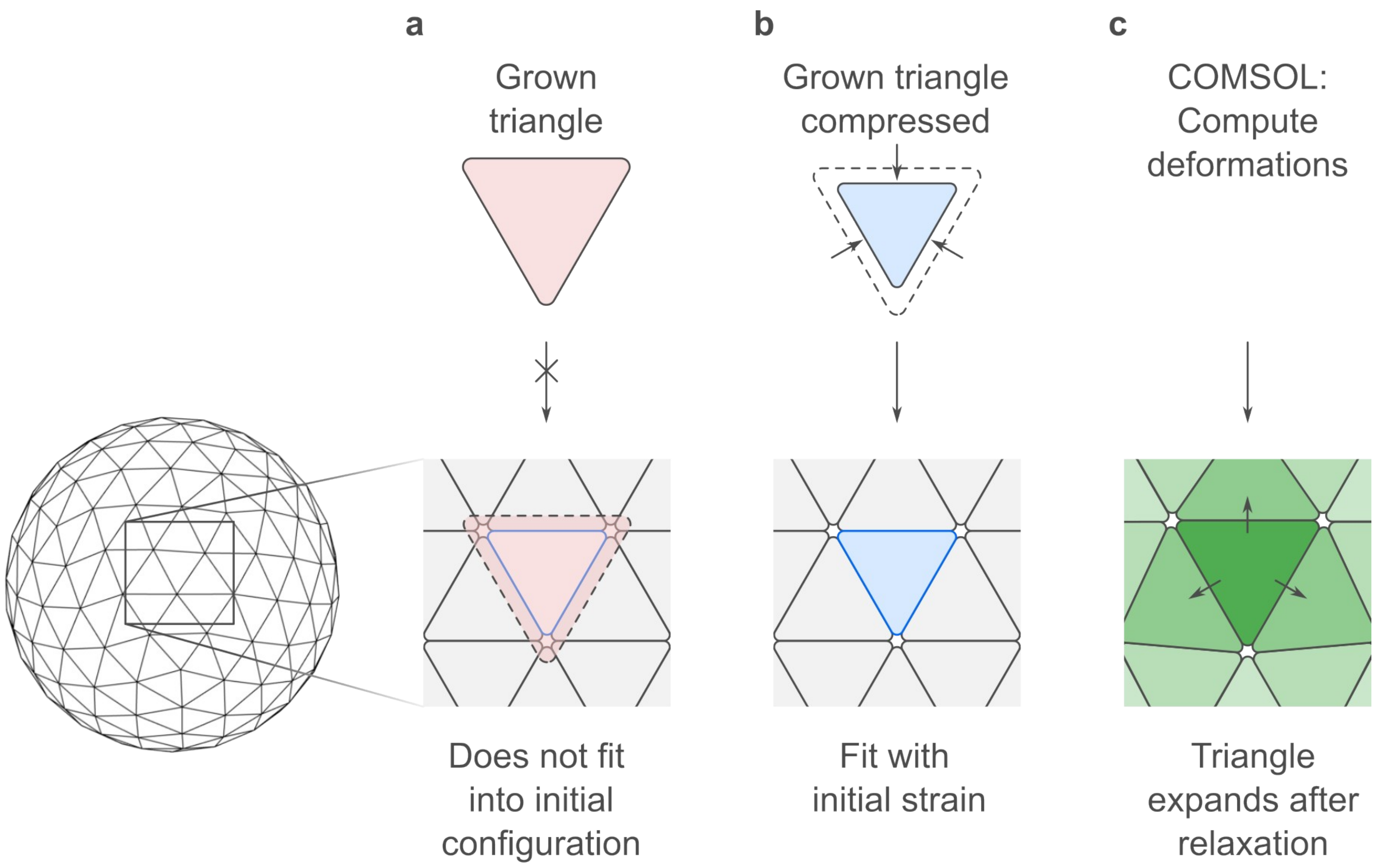
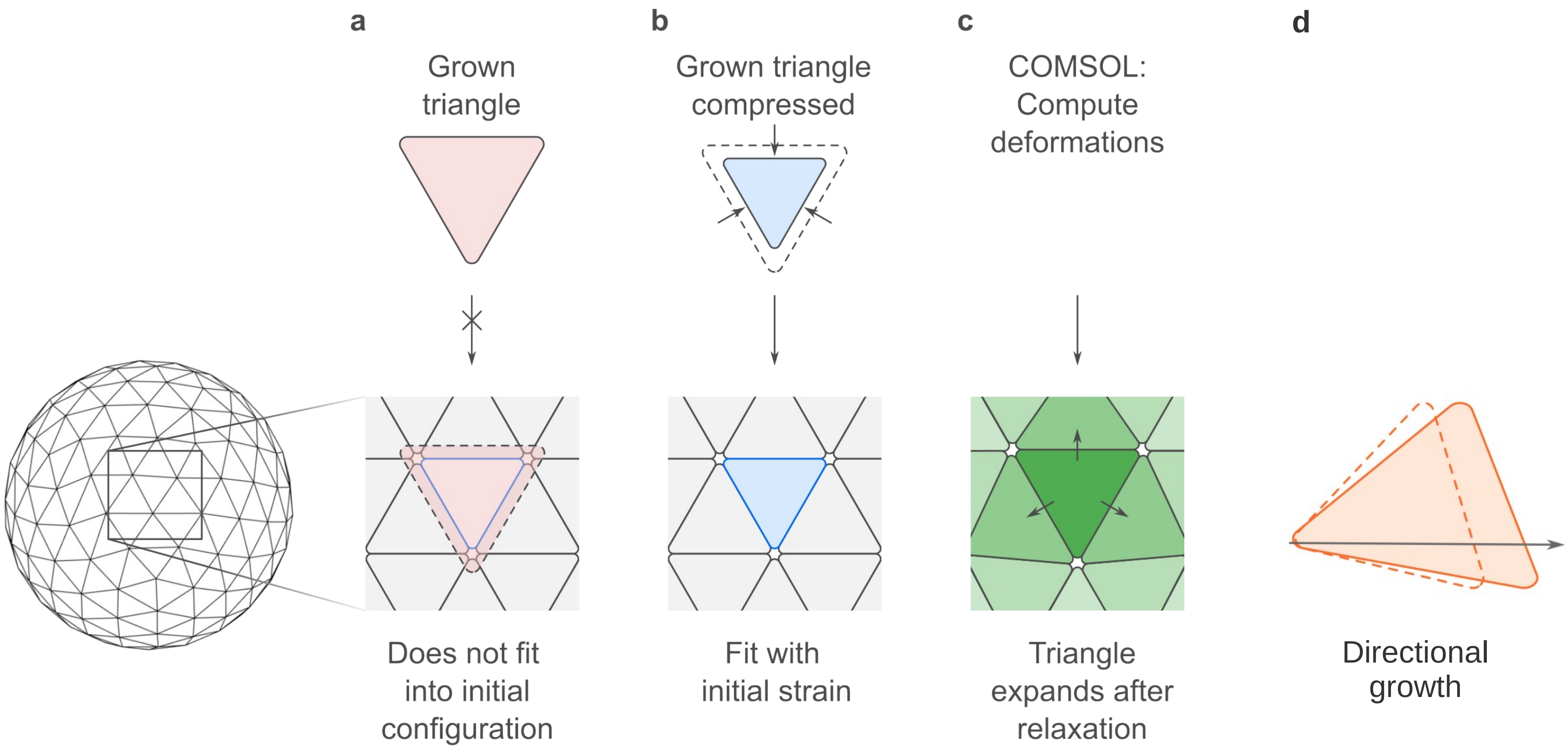
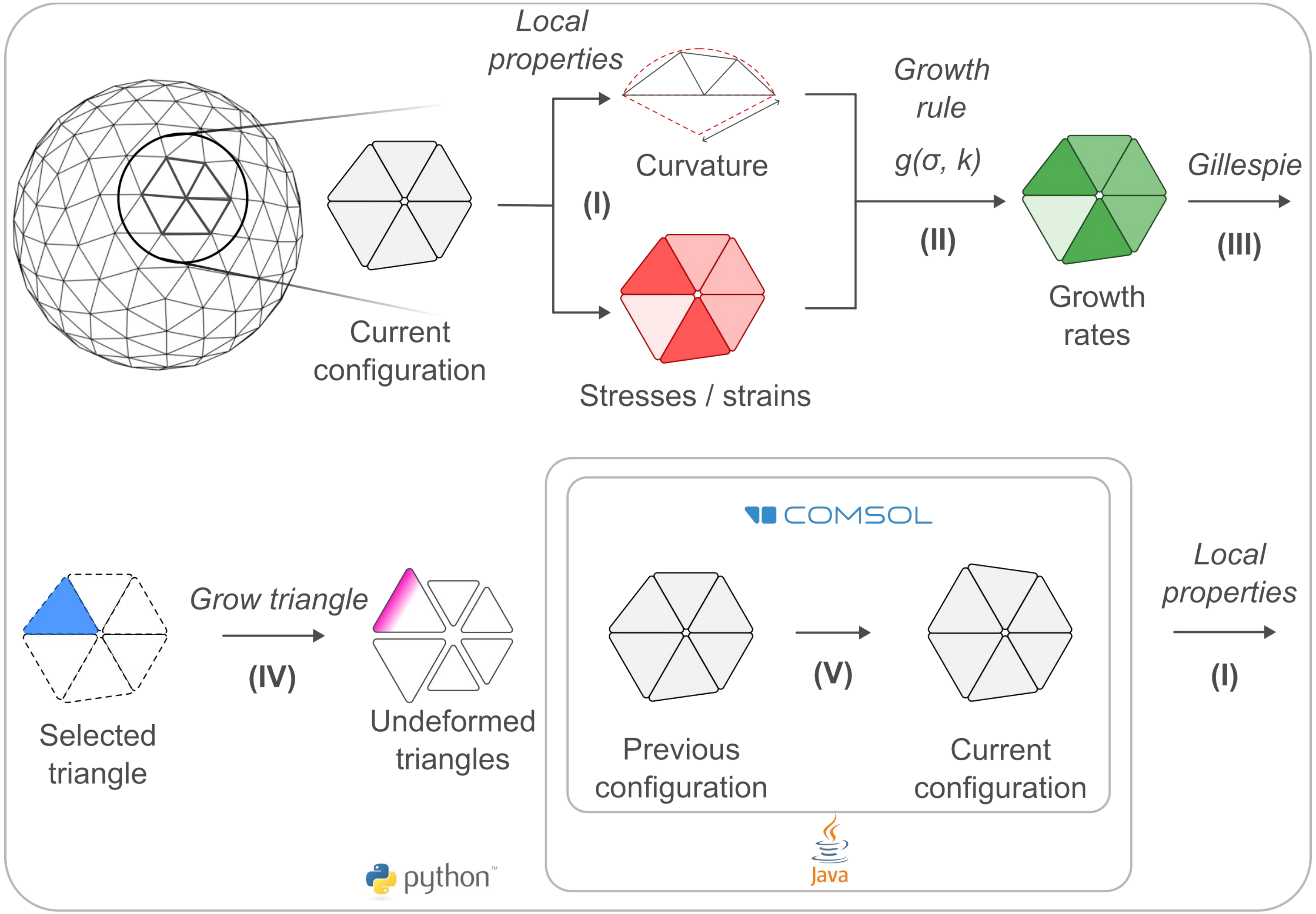


Finite-element-based Model



Simulation flowchart



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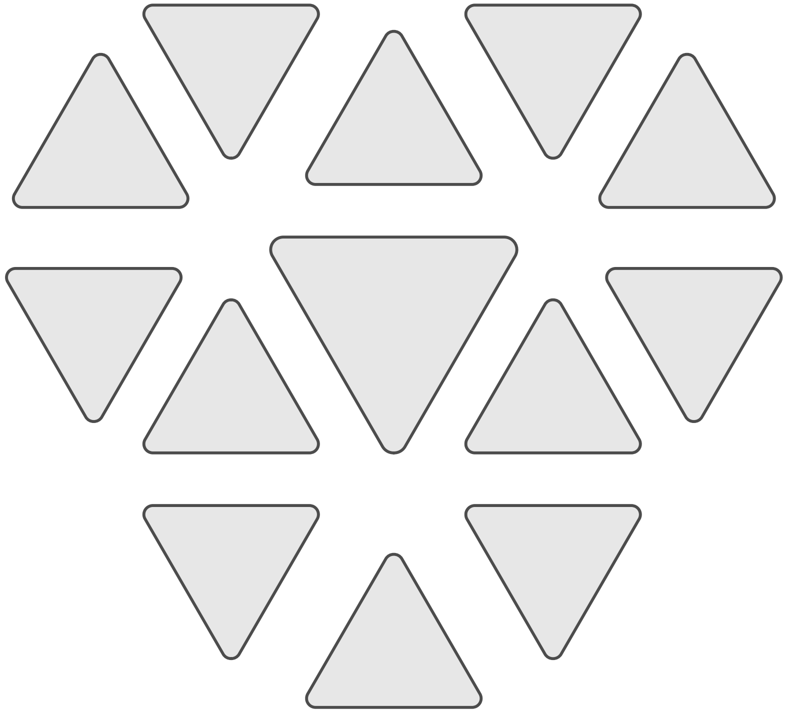
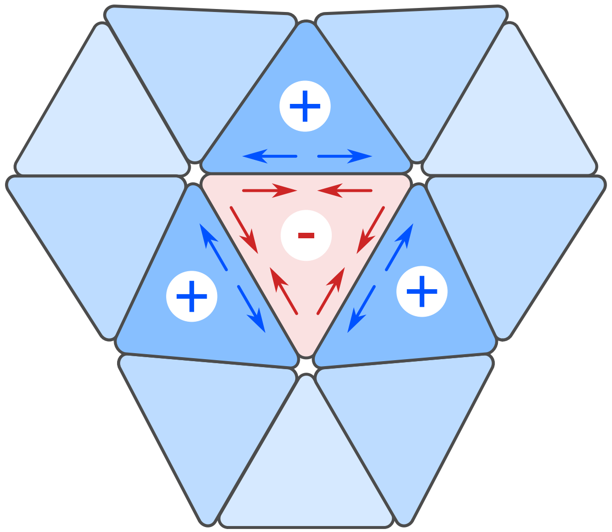
Observable: Surface stresses





Size mismatch of elements

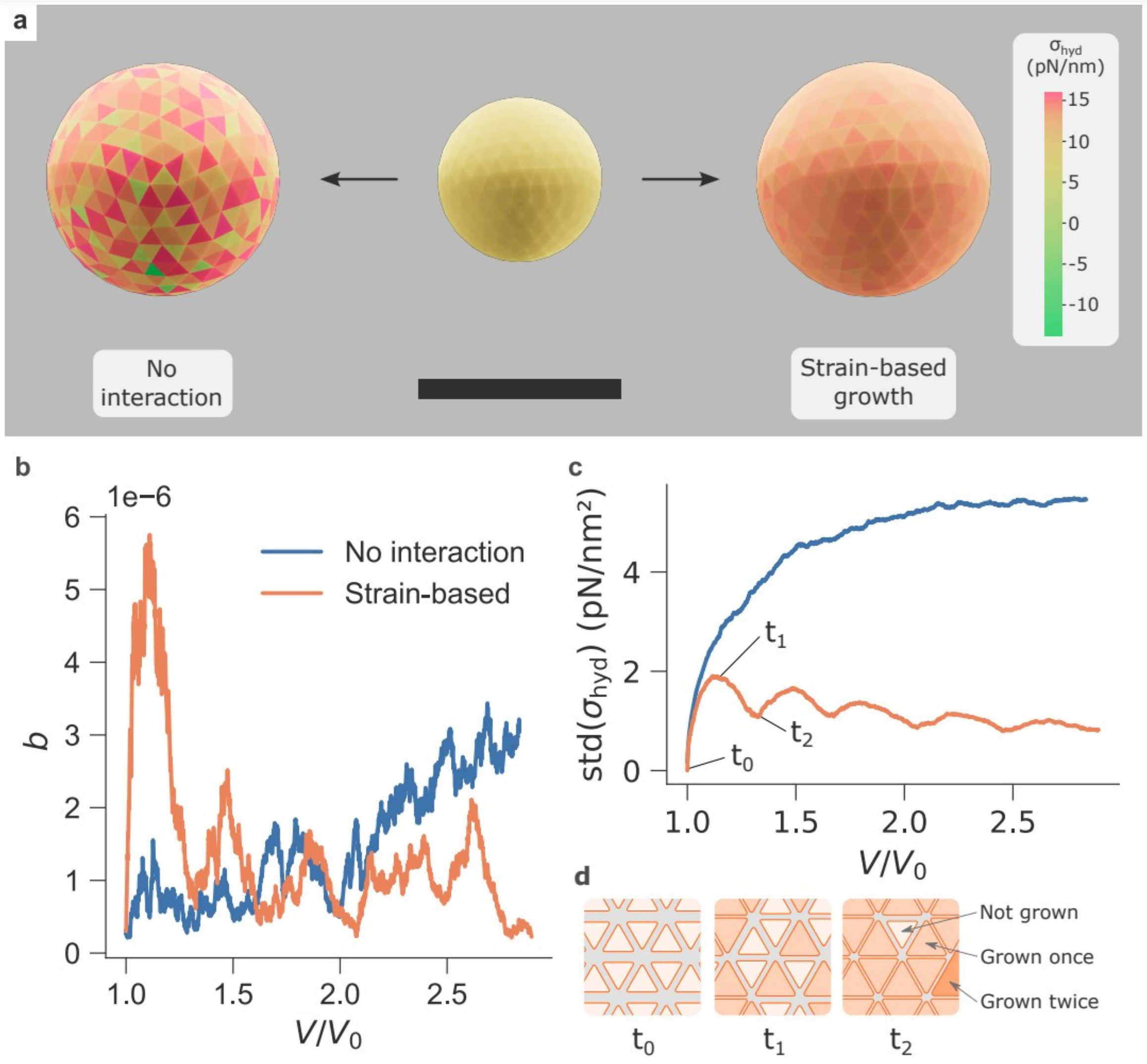
→ High compressive and tensile stresses

→ Affects mechanical stability

Random vs. strain-based growth

Strain-based growth rates:

$$\lambda^{(e)} = -\lambda_0 + \lambda_1 \varepsilon_h^{(e)}$$



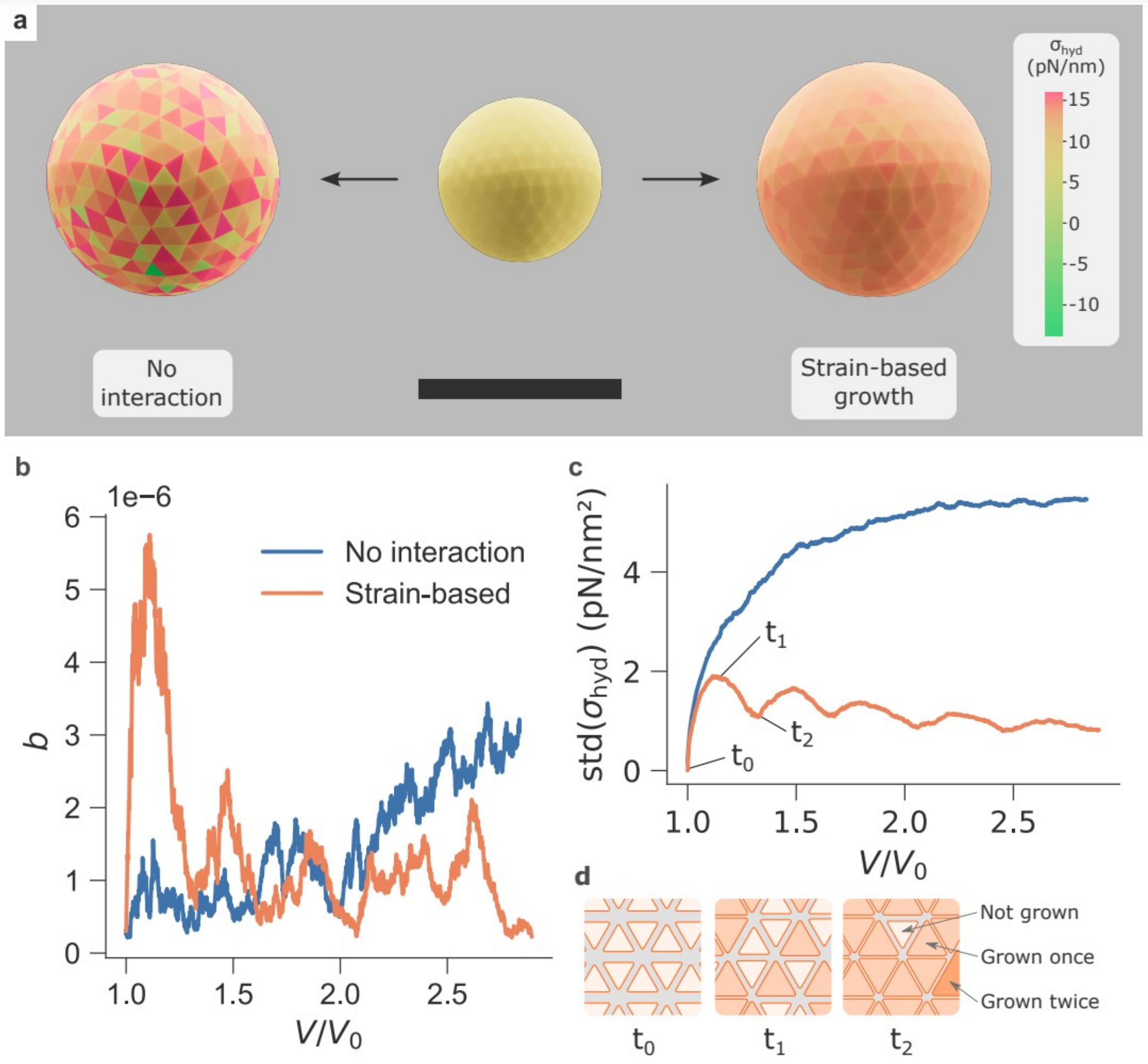
Random vs. strain-based growth

Strain-based growth rates:

$$\lambda^{(e)} = -\lambda_0 + \lambda_1 \varepsilon_h^{(e)}$$

Random
→ Spherical shape
→ High surface stresses

Strain-based
→ Spherical shape
→ Moderate surface stresses



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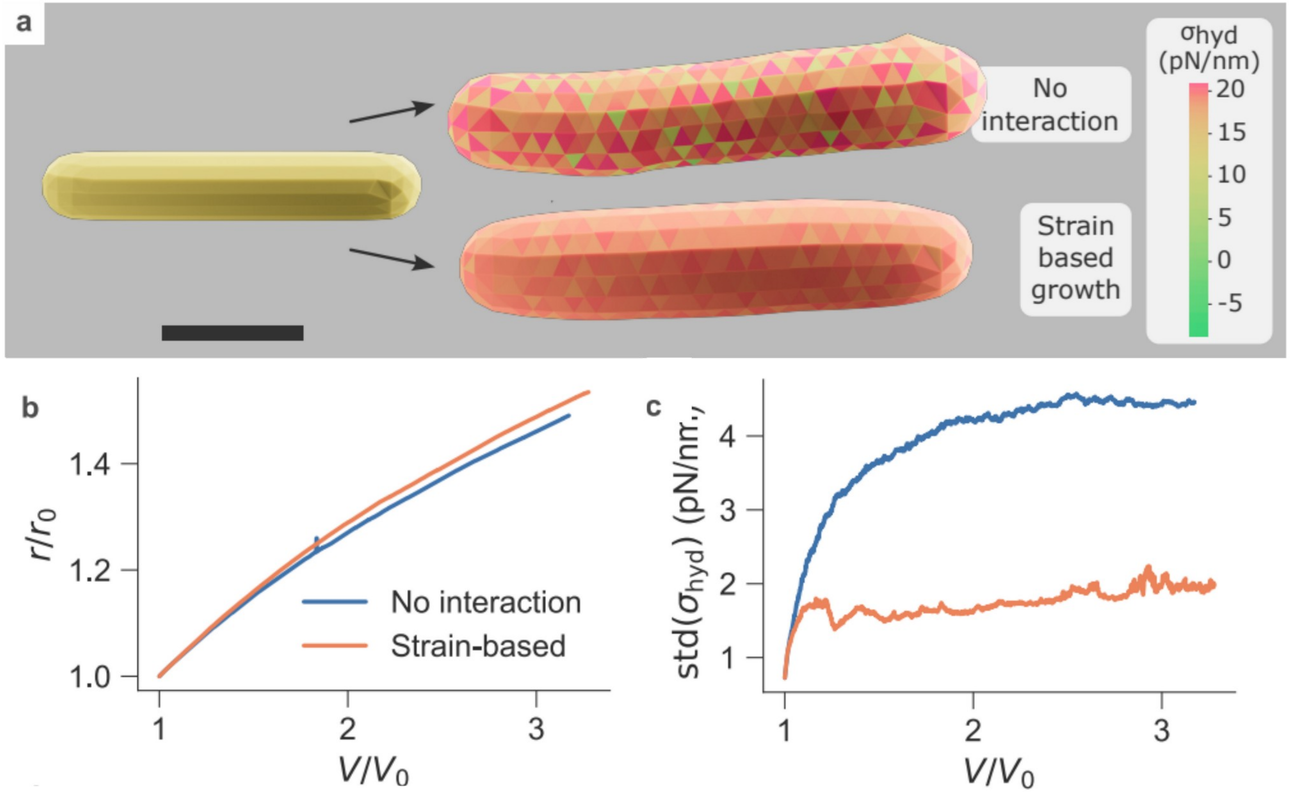

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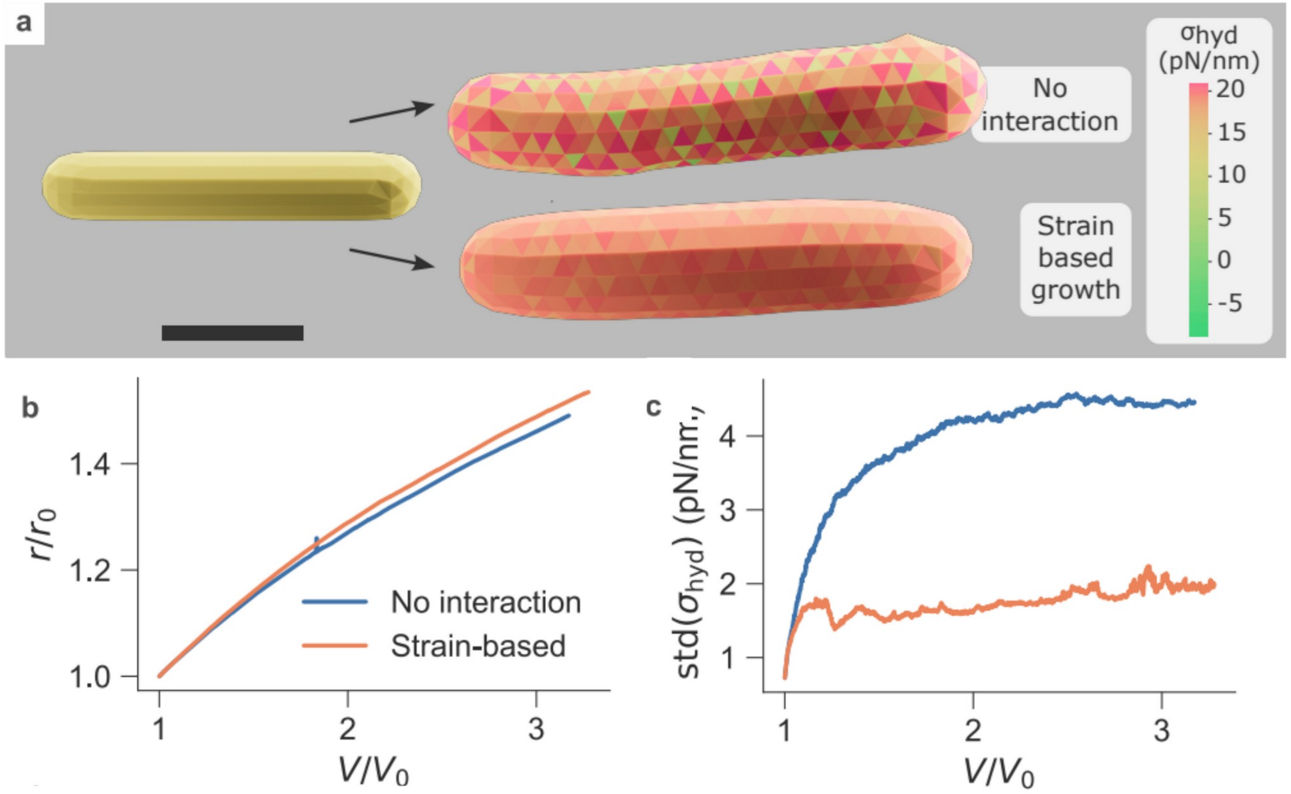
$$\lambda^{(e)} = -\lambda_0 + \lambda_1 \varepsilon_h^{(e)}$$

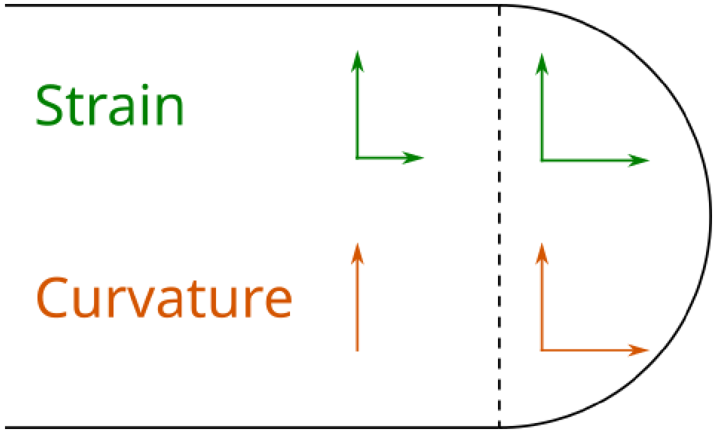
Random
→ Spherical shape
→ High stresses

Strain-based
→ Spherical shape
→ Moderate stresses

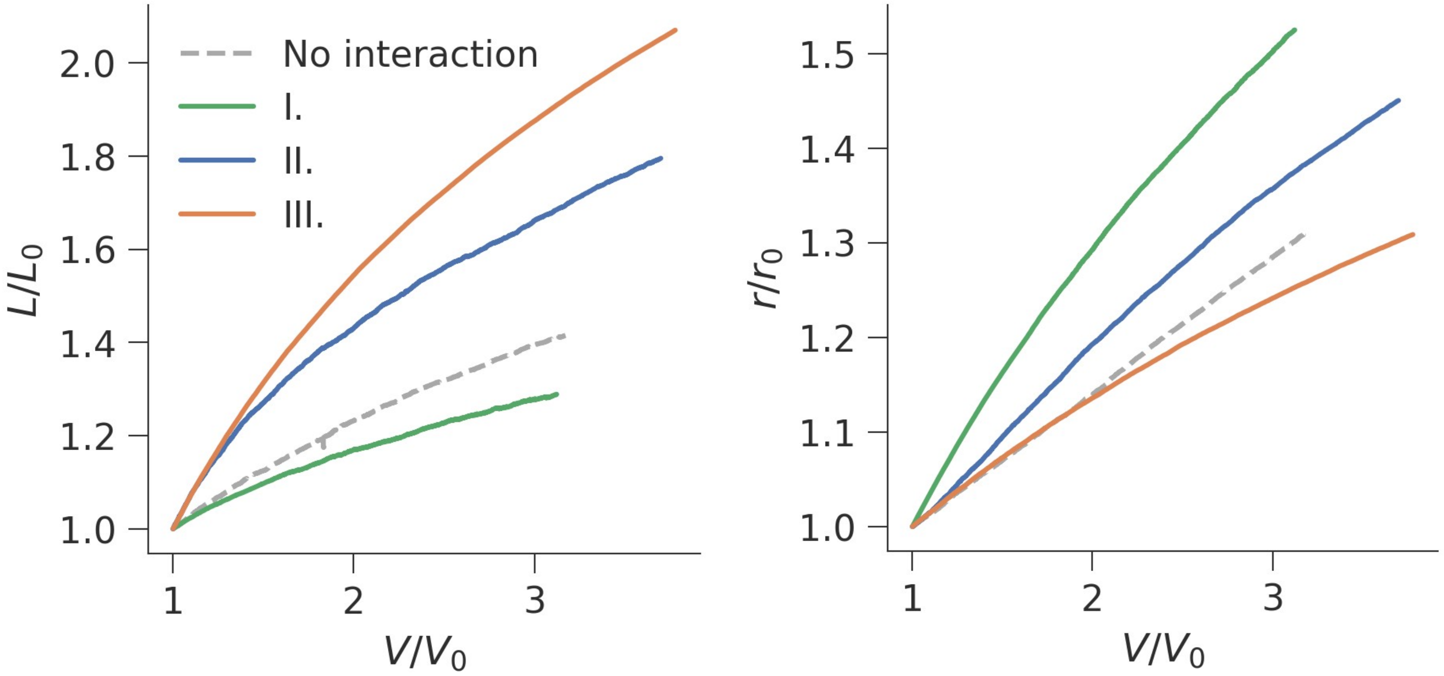
⟹ Radius is <u>not conserved</u>



Directional Growth: Strain / Curvature

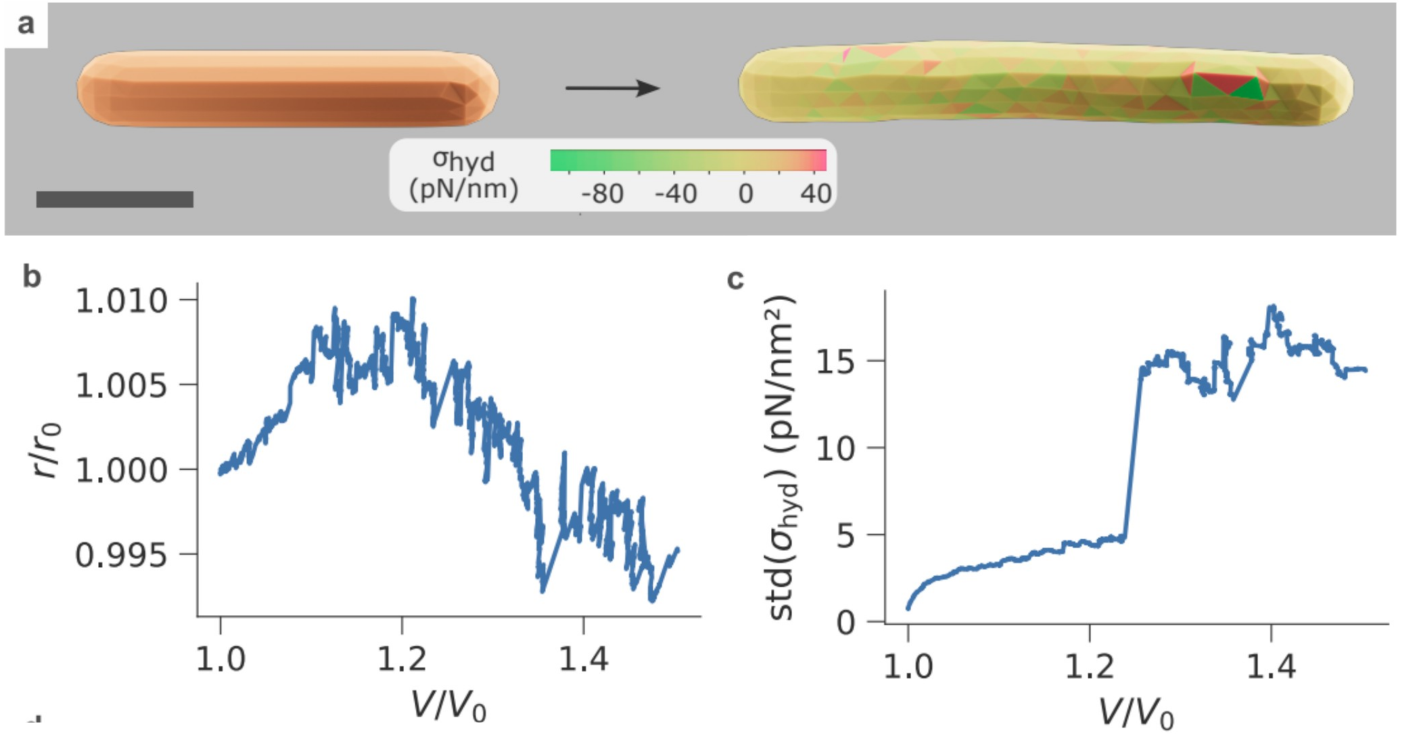


	Location	Direction
I.	Strain	Strain
II.	Curvature	Strain
III.	Curvature	Curvature



Correction mechanism

Combination
longitudinal: +
circumferential: -



→ Elongation
→ Radius is conserved
→ Problem: Large stresses

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Summary

- Implemented two physical models of the bacterial shell
- Limitations of the spring-based model
- Solved with finite-element-based model
- Strain-based growth improved the mechanical stability
- Importance of a correction mechanism

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Outlook

- Understanding high stresses
- Explore the parameter space
  - Gram-positive bacteria: Higher pressures, thicker cell wall
  - Pressure changes during growth
- Explore other geometries

Thank you

Appendix

$$Y = \frac{2}{\sqrt{3}} k_s,$$

$$\kappa_{\mathrm{b}} = \frac{\sqrt{3}}{2} k_{\mathrm{b}},$$

$$\kappa_b = \frac{Et^3}{12(1-\nu)}$$

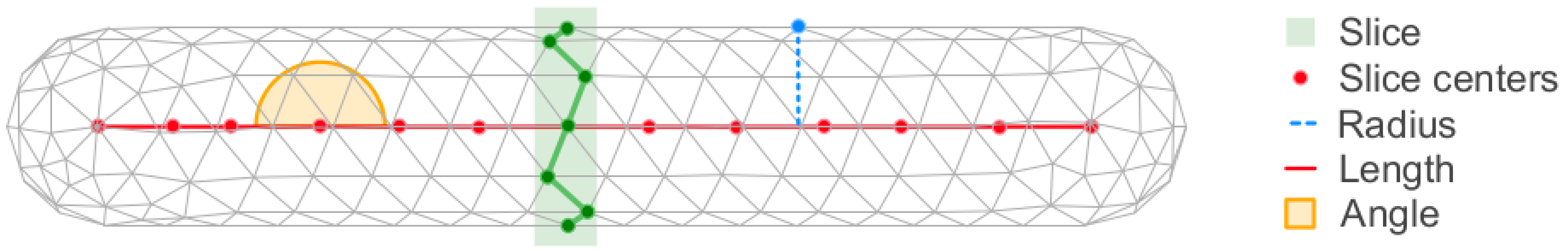
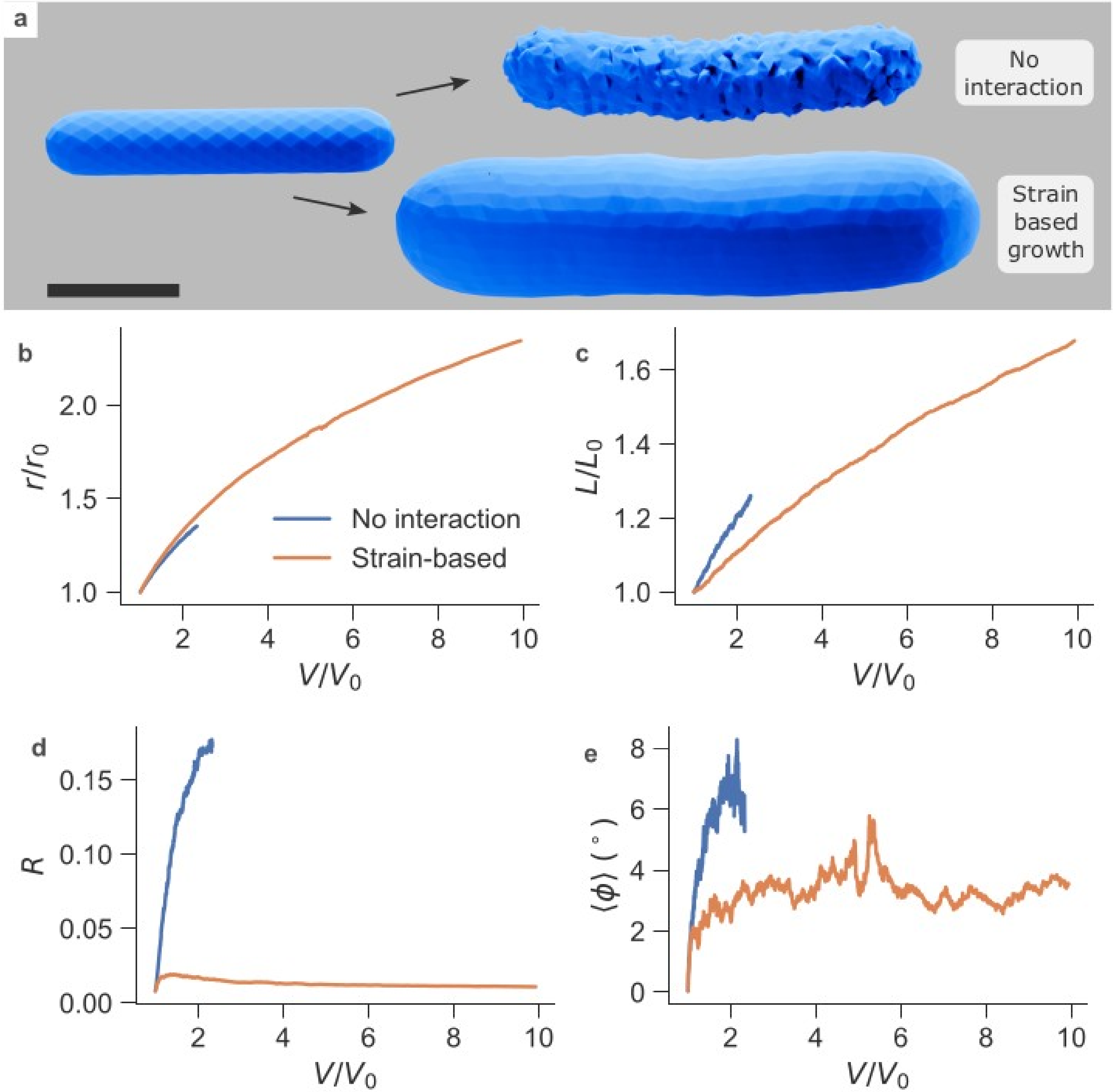
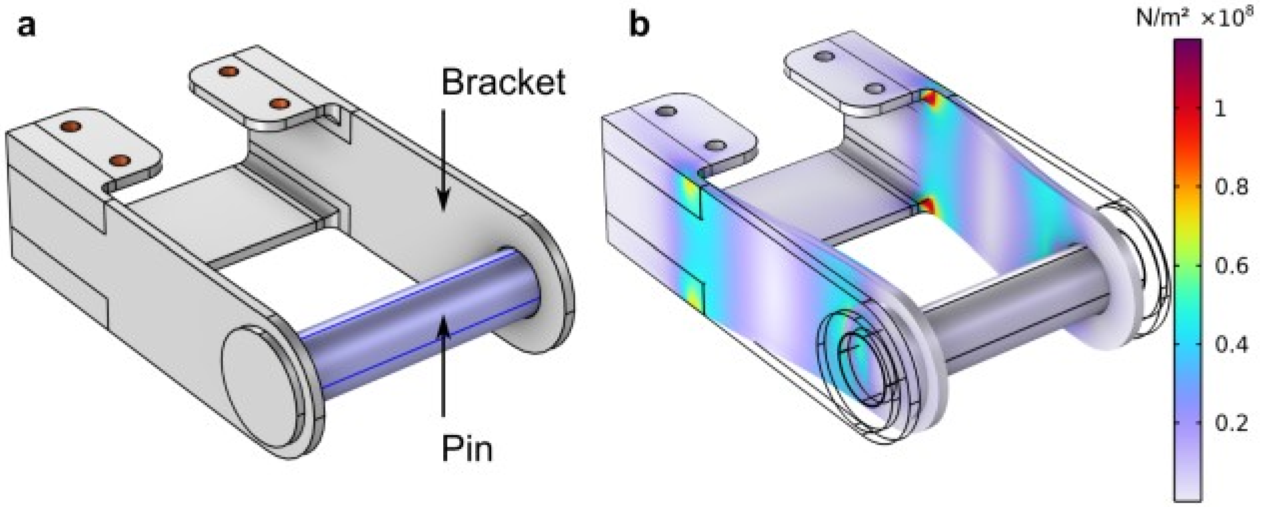
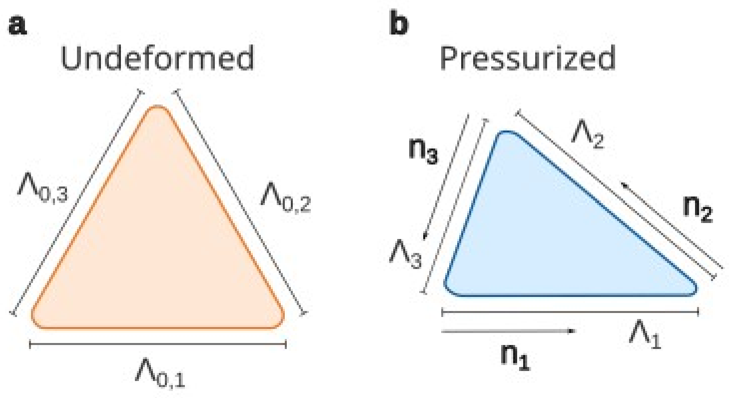


Figure 2.3.4: Computing length, radius and bending angle of the rod-shaped shell.
The shell is divided into slices (green) along its length. At initialization, each vertex is assigned a slice. The gravitational centers of the slices (red dots) can be computed at any point in the simulation. Radius, length and bending angles are computed from the line connecting the slice centers.


a
No interaction
Strain based growth
b
r/r0
V/V0
No interaction
Strain-based
c
L/L0
V/V0
d
R
V/V0
e
⟨ϕ⟩ (°)
V/V0

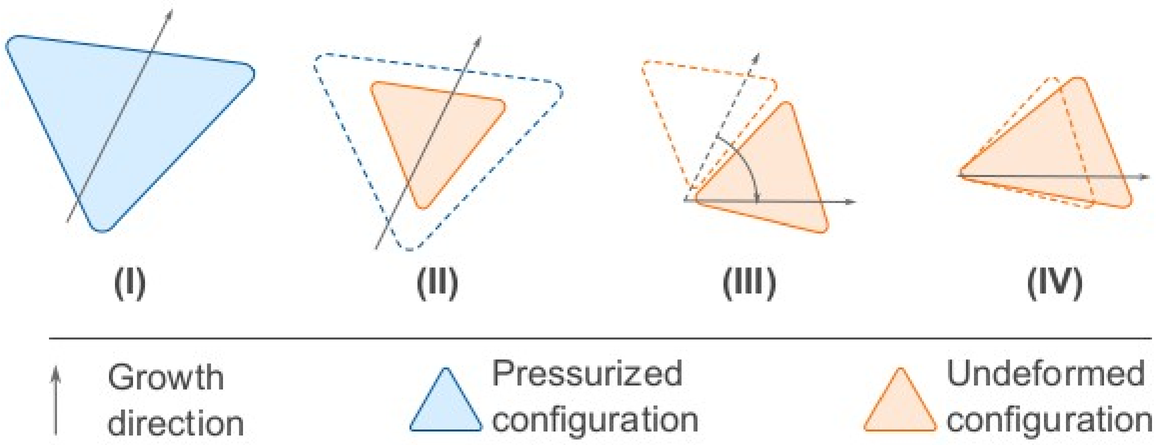

a
Bracket
Pin
b
N/m² ×10⁸
1
0.8
0.6
0.4
0.2

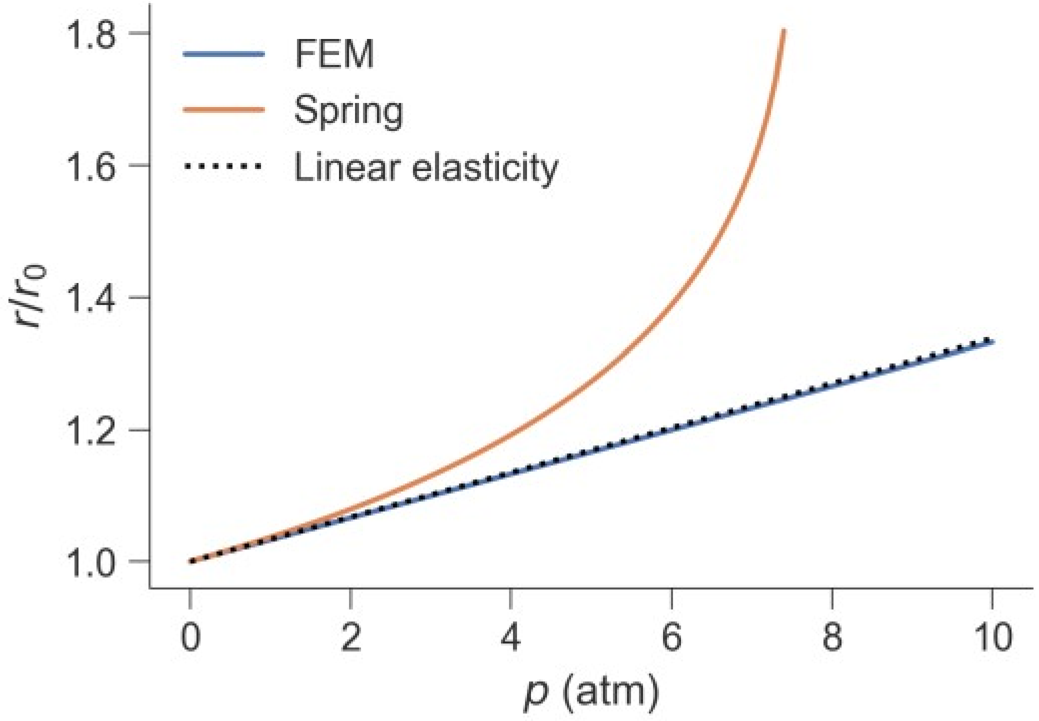


$$\varepsilon(\vec{n}^{(i)}) = \frac{\Lambda_i - \Lambda_{i,0}}{\Lambda_i}$$

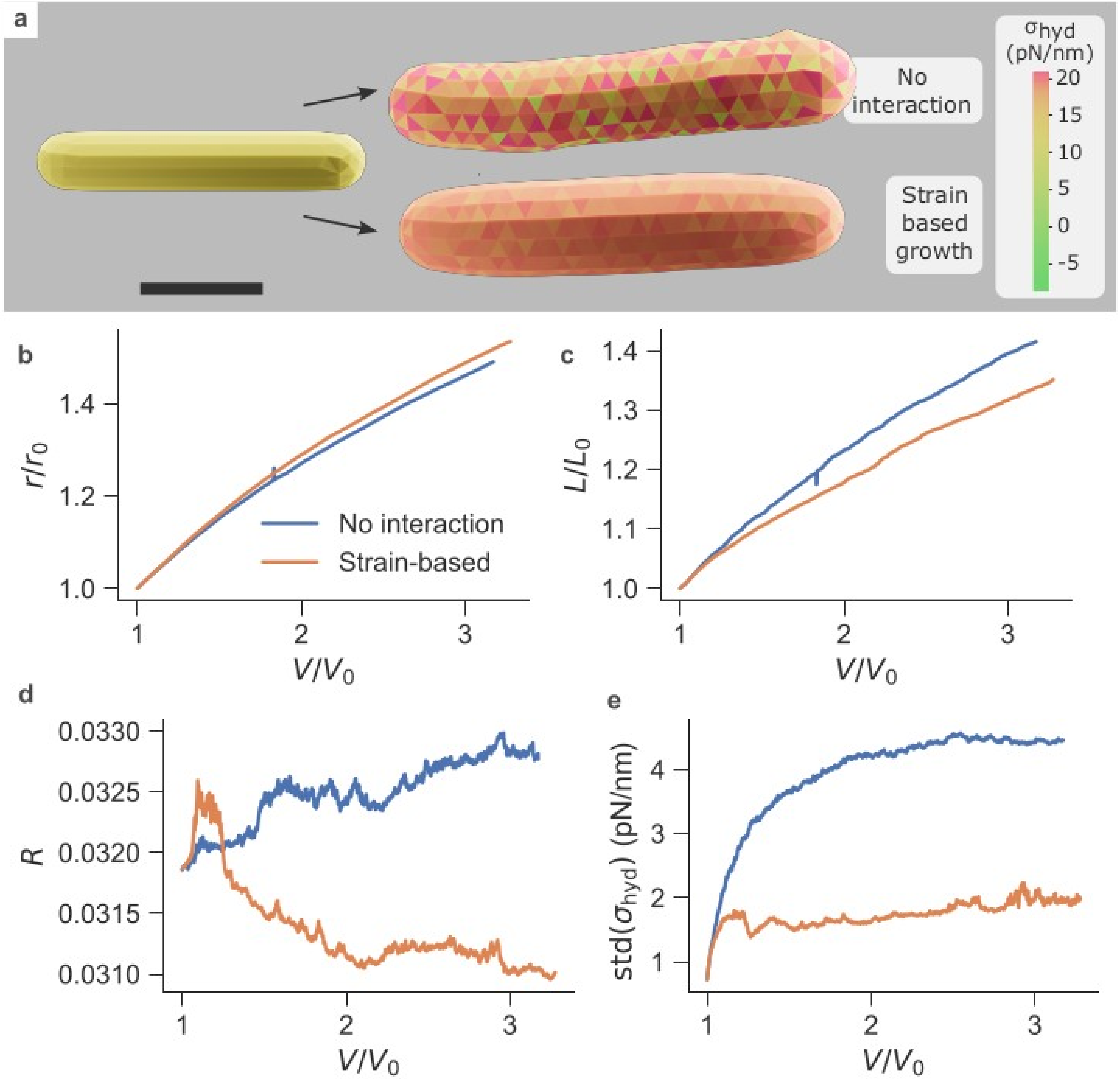
$$\varepsilon_{\text{direction}}(\vec{n}^{(i)}) = \varepsilon_{kl} n_k^{(i)} n_l^{(i)},$$

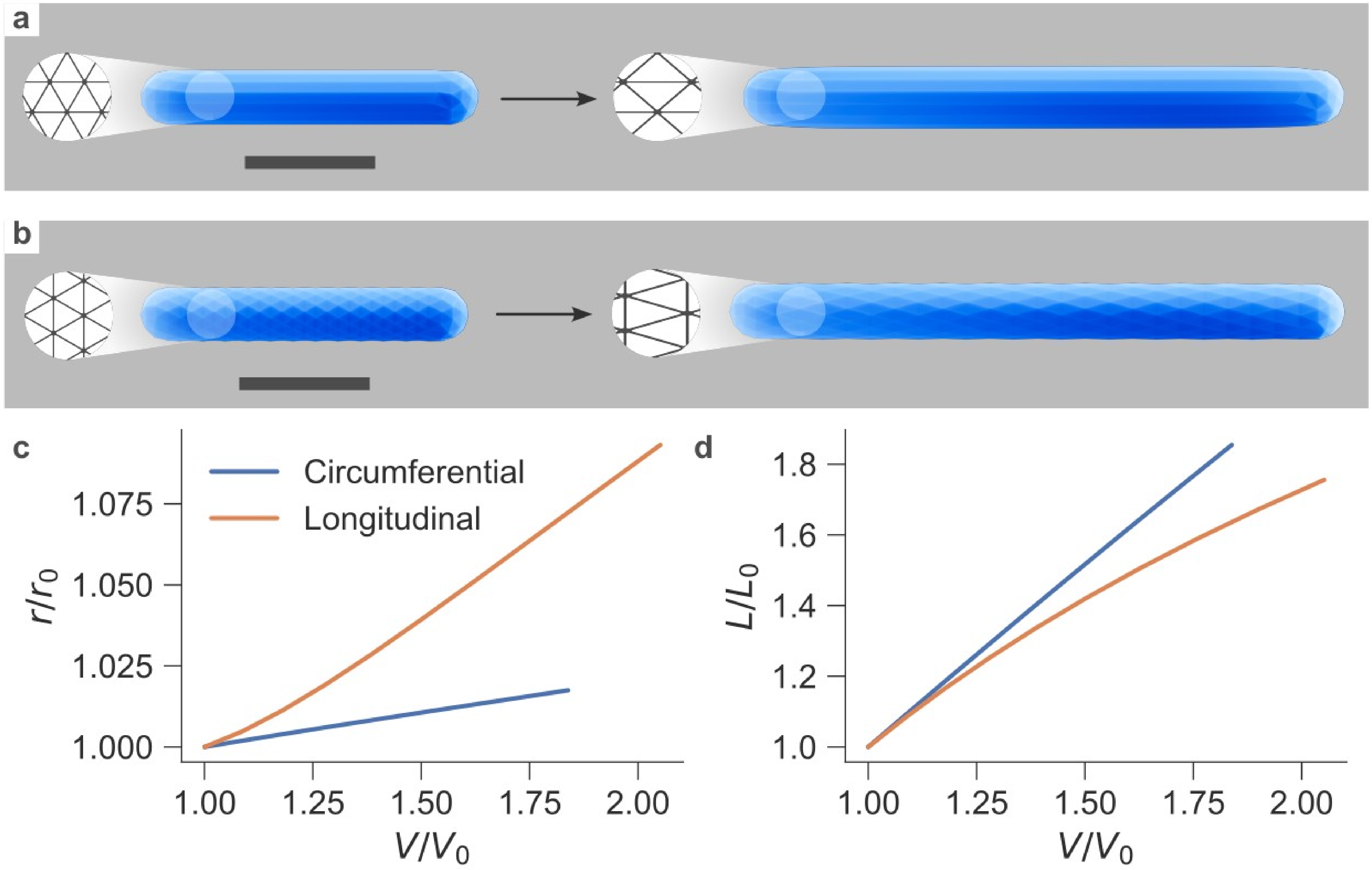
$$\begin{bmatrix} \varepsilon_{\text{direction}}(\vec{n}^{(1)}) \\ \varepsilon_{\text{direction}}(\vec{n}^{(2)}) \\ \varepsilon_{\text{direction}}(\vec{n}^{(3)}) \end{bmatrix} = \begin{bmatrix} n_1^{(1)} n_1^{(1)} & n_1^{(1)} n_2^{(1)} & n_2^{(1)} n_2^{(1)} \\ n_1^{(2)} n_1^{(2)} & n_1^{(2)} n_2^{(2)} & n_2^{(2)} n_2^{(2)} \\ n_1^{(3)} n_1^{(3)} & n_1^{(3)} n_2^{(3)} & n_2^{(3)} n_2^{(3)} \end{bmatrix} \cdot \begin{bmatrix} \varepsilon_{11} \\ 2\varepsilon_{12} \\ \varepsilon_{22} \end{bmatrix}$$


(I)
(II)
(III)
(IV)
Growth direction
Pressurized configuration
Undeformed configuration

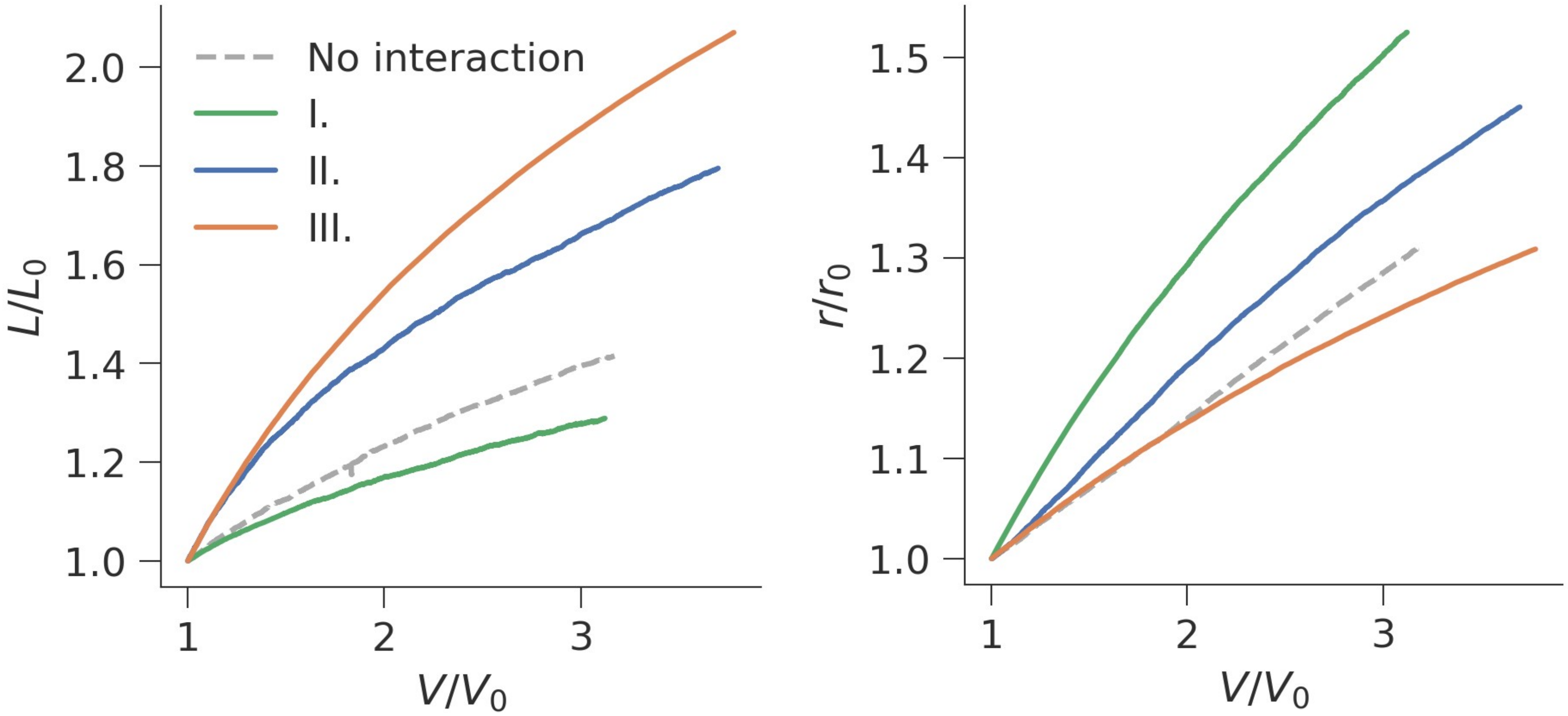


FEM
Spring
Linear elasticity
1.8
1.6
1.4
1.2
1.0
r/r_0
0
2
4
6
8
10
p (atm)

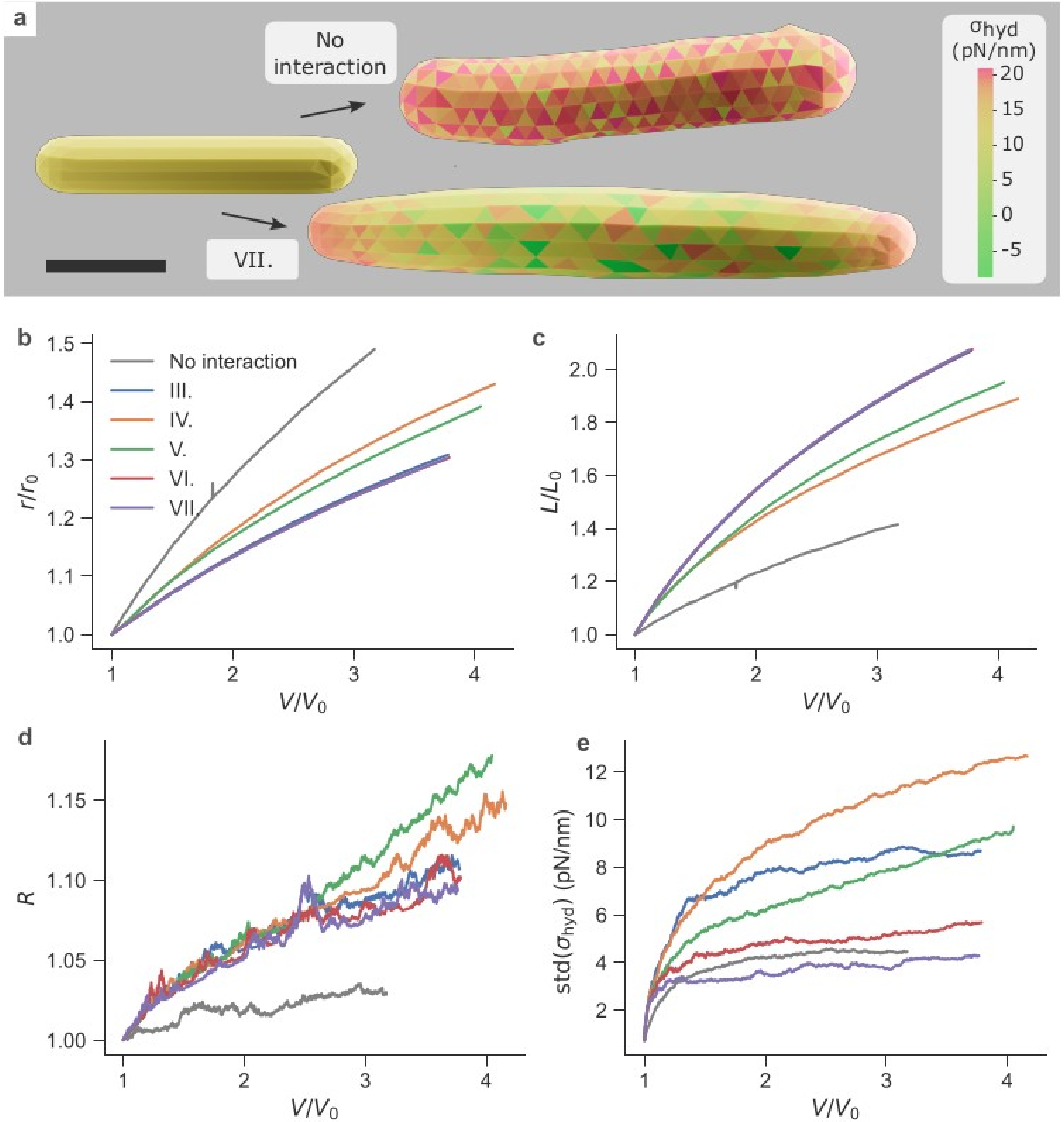

a
No interaction
Strain based growth
σhyd (pN/nm)
20
15
10
5
0
-5
b
r/r0
1.4
1.2
1.0
No interaction
Strain-based
1
2
3
V/V0
c
L/L0
1.4
1.3
1.2
1.1
1.0
1
2
3
V/V0
d
R
0.0330
0.0325
0.0320
0.0315
0.0310
1
2
3
V/V0
e
std(σhyd) (pN/nm)
4
3
2
1
1
2
3
V/V0



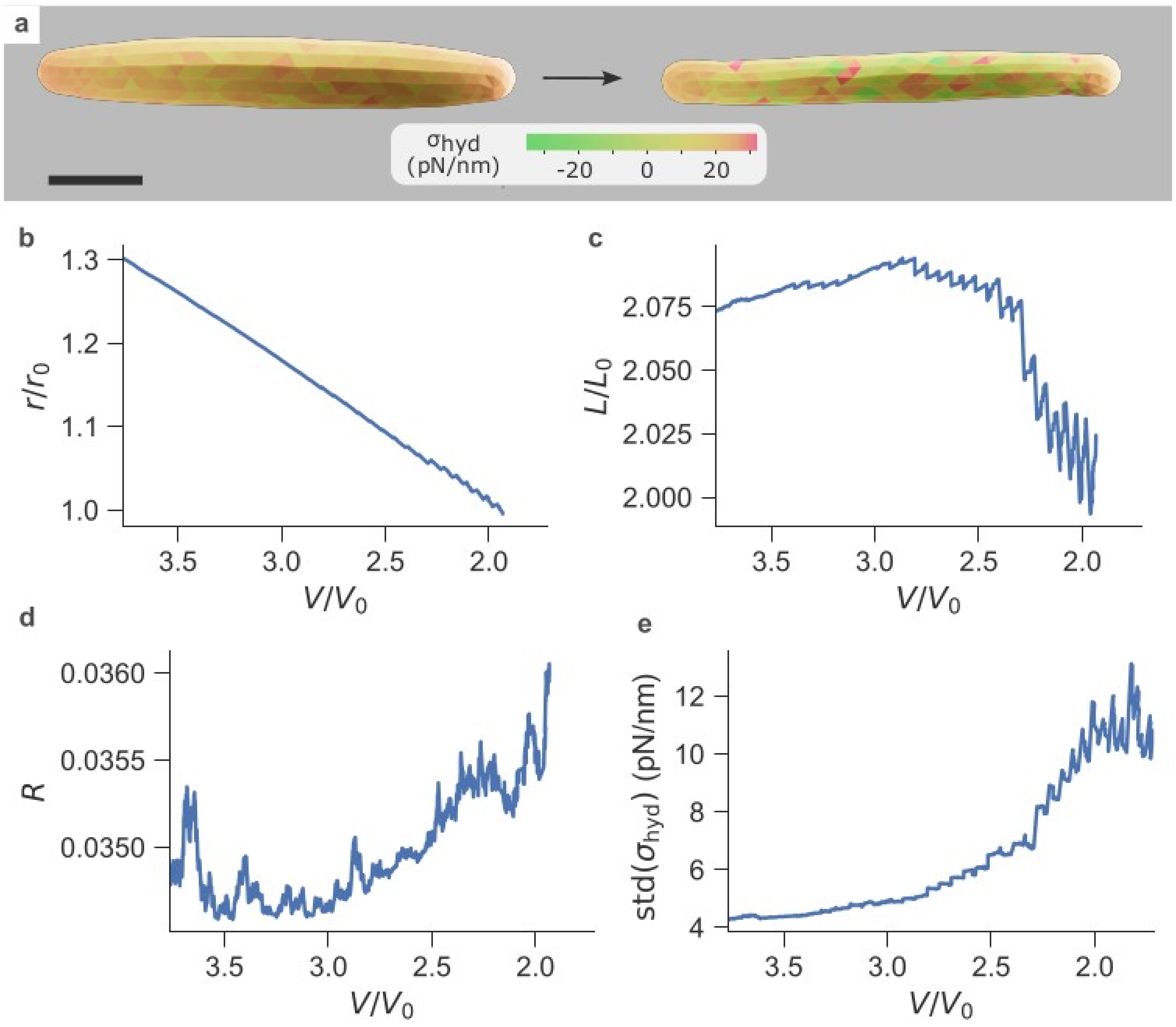
a
b
c
Circumferential
Longitudinal
r/r_0
1.000
1.025
1.050
1.075
1.00
1.25
1.50
1.75
2.00
V/V_0
d
L/L_0
1.0
1.2
1.4
1.6
1.8
1.00
1.25
1.50
1.75
2.00
V/V_0

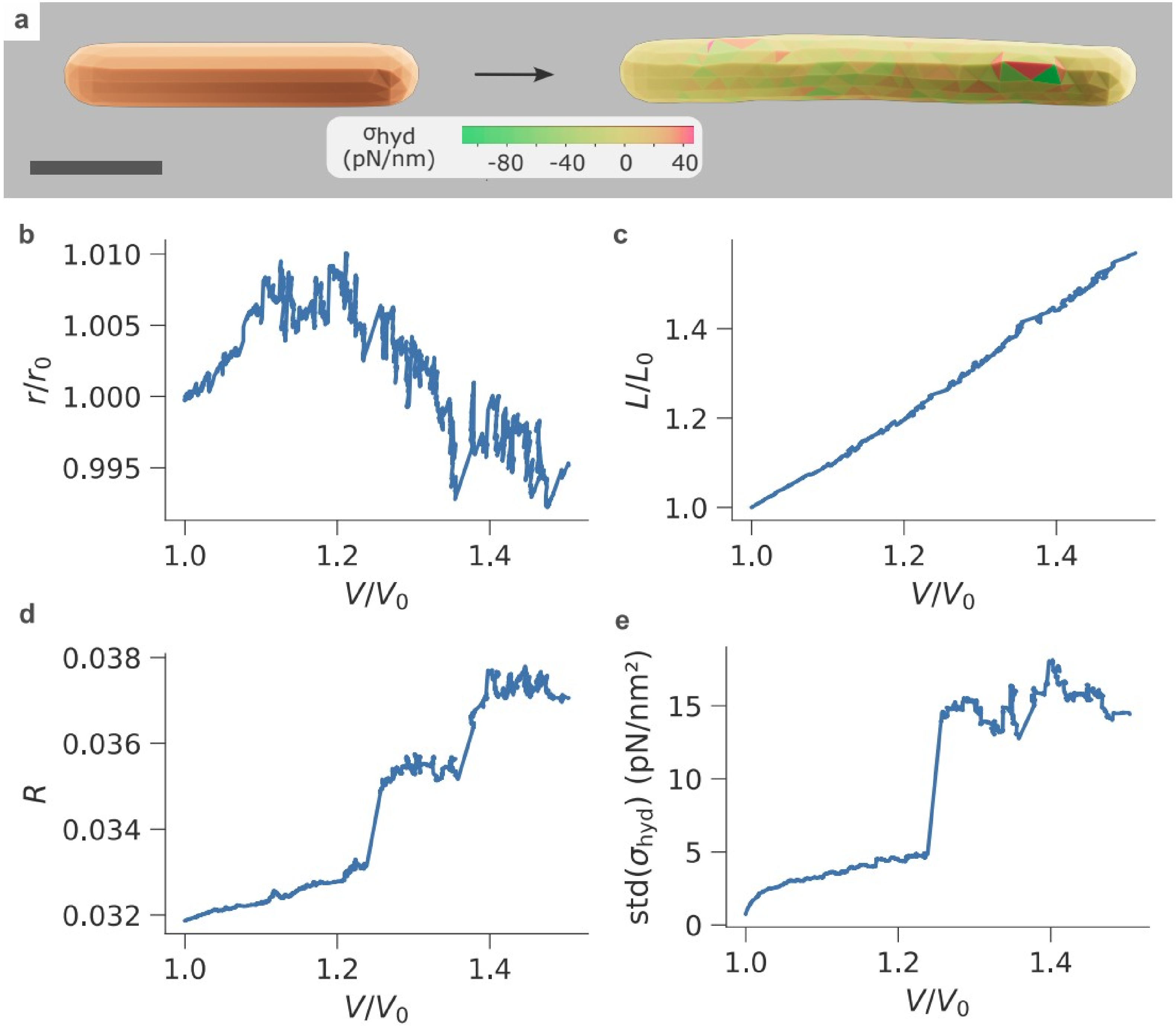


	Growth reaction rates	Growth direction
I.	$\lambda_0 + \lambda_1 \varepsilon_{\min} - \lambda_2 \varepsilon_{\max}$	$\varepsilon_{\min}$
II.	$\lambda_0 + \lambda_1 K_{\min}$	$\varepsilon_{\min}$
III.	$\lambda_0 + \lambda_1 K_{\min}$	$K_{\min}$

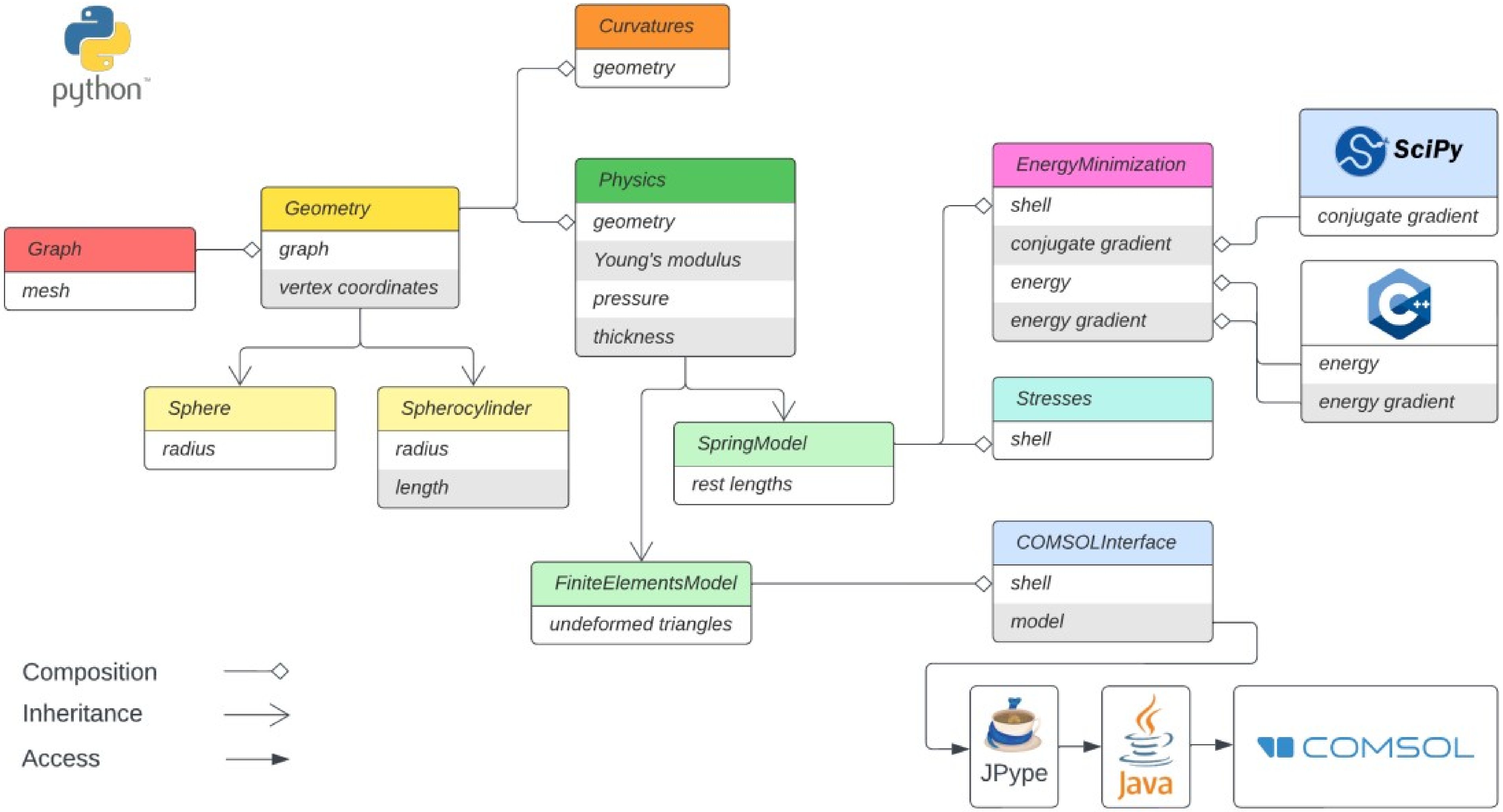


	Growth reaction rates	Growth direction
IV.	$-\lambda_0 + \lambda_1 K_{\min} + \lambda_2 \varepsilon_{\text{hyd}}$	$\varepsilon_{\min}$
V.	$-\lambda_0 + \lambda_1 K_{\min} + \lambda_2 \varepsilon_{\min}$	$\varepsilon_{\min}$
VI.	$-\lambda_0 + \lambda_1 K_{\min} + \lambda_2 \varepsilon_{\text{hyd}}$	$K_{\min}$
VII.	$-\lambda_0 + \lambda_1 K_{\min} + \lambda_2 \varepsilon_{\min}$	$K_{\min}$

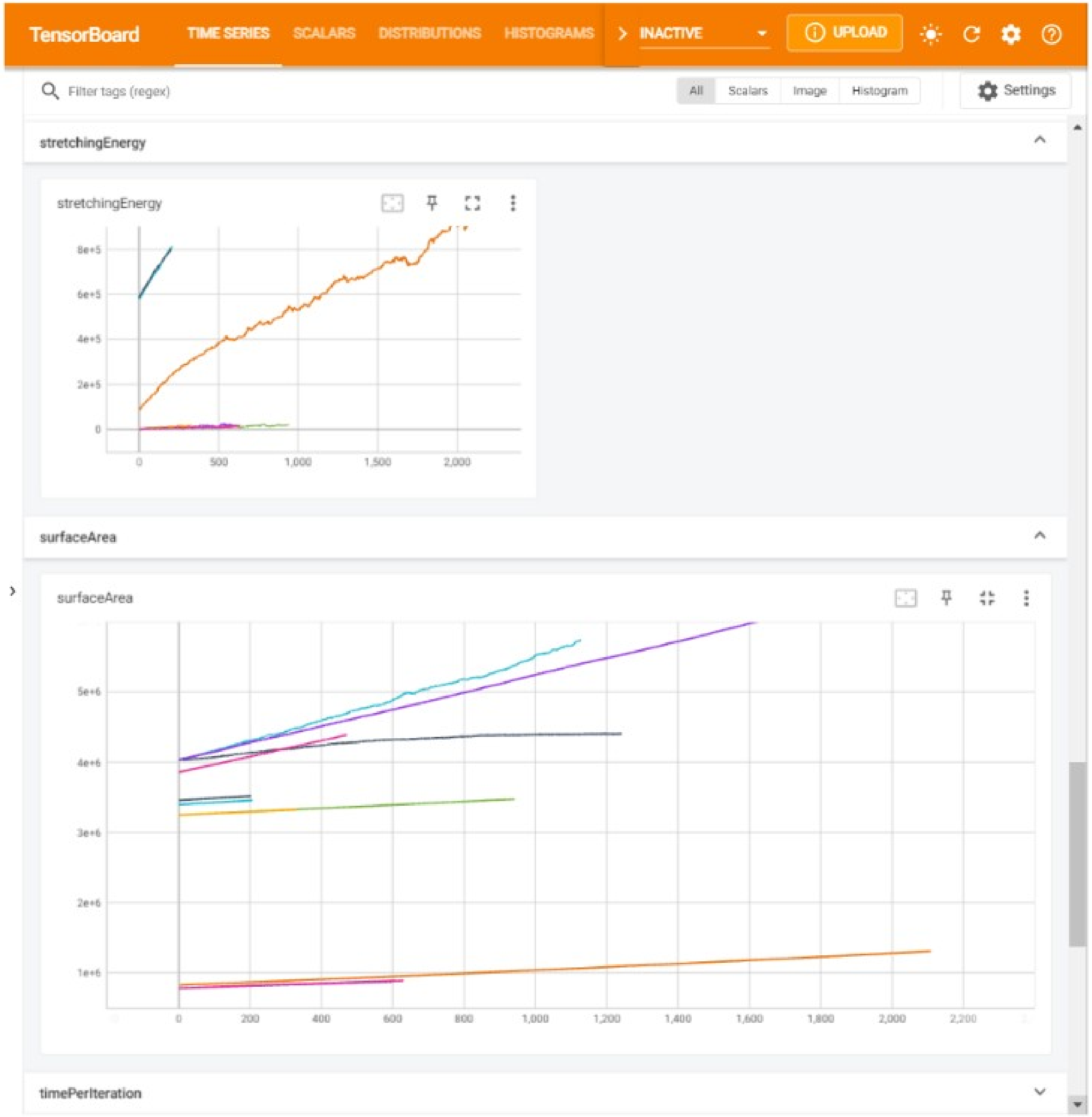

a
σhyd
(pN/nm)
-20
0
20
b
1.3
1.2
1.1
1.0
r/r_0
3.5
3.0
2.5
2.0
V/V_0
c
2.075
2.050
2.025
2.000
L/L_0
3.5
3.0
2.5
2.0
V/V_0
d
0.0360
0.0355
0.0350
R
3.5
3.0
2.5
2.0
V/V_0
e
12
10
8
6
4
std(σ_{hyd}) (pN/nm)
3.5
3.0
2.5
2.0
V/V_0

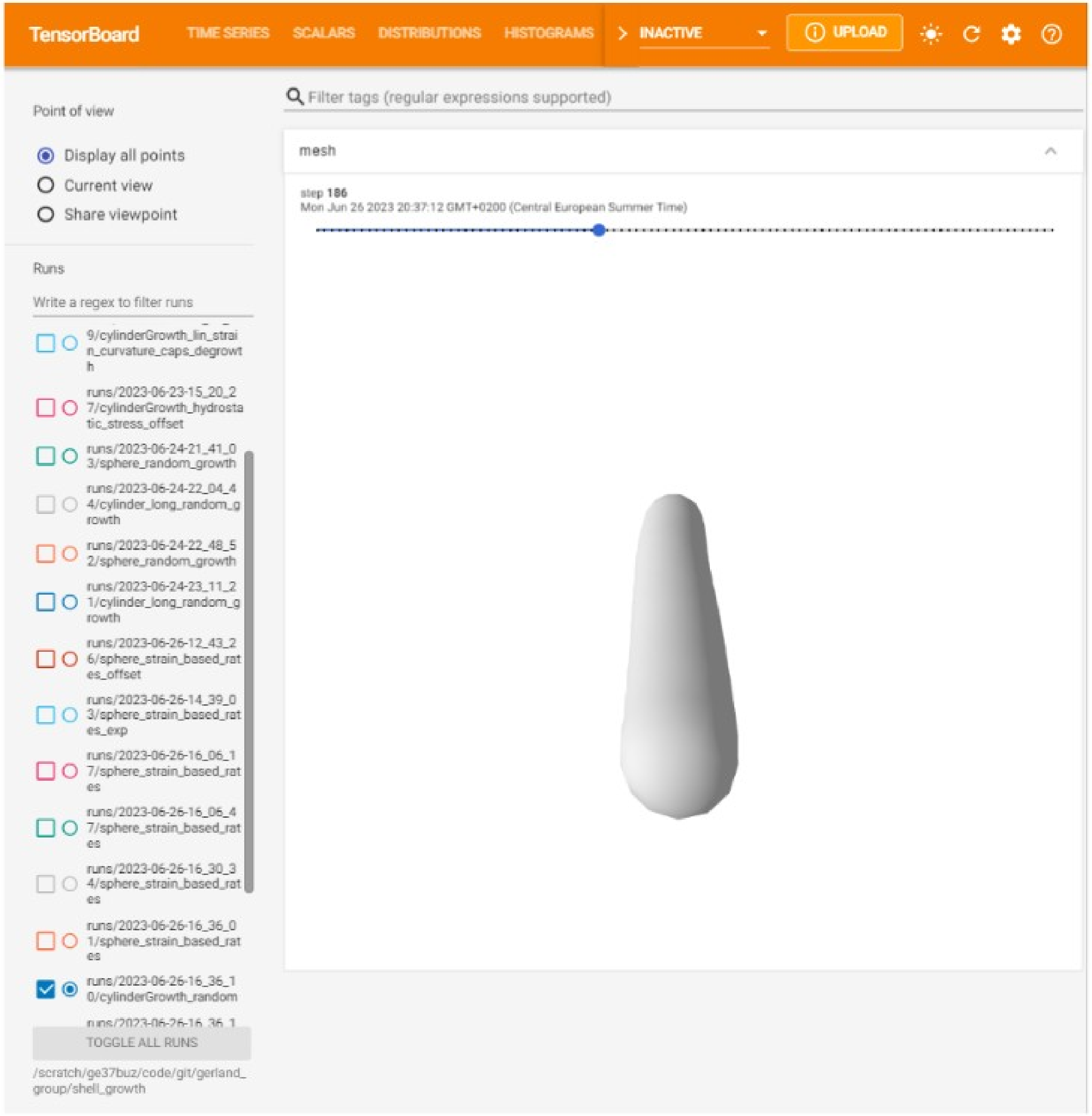


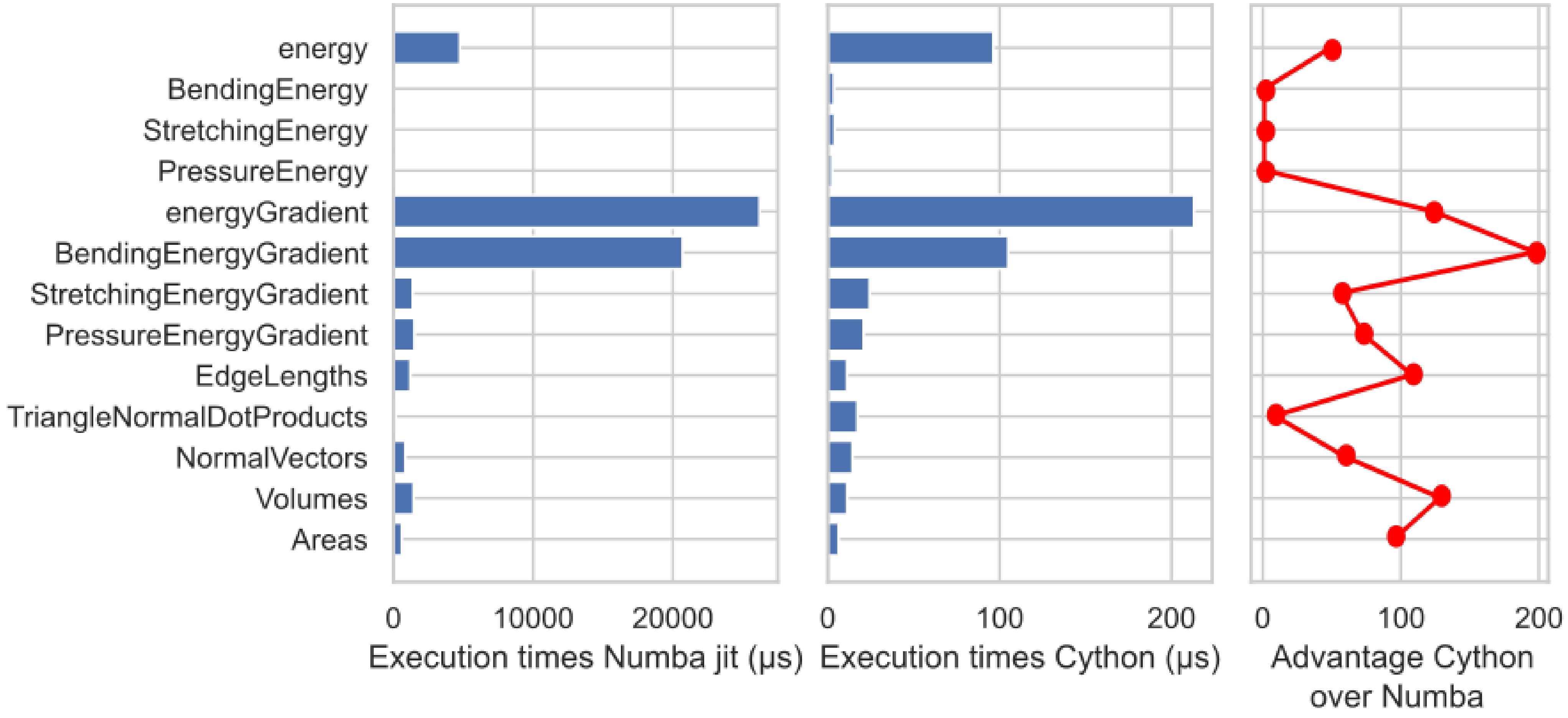
a
σhyd
(pN/nm)
-80 -40 0 40
b
r/r_0
1.010
1.005
1.000
0.995
1.0 1.2 1.4
V/V_0
c
L/L_0
1.4
1.2
1.0
1.0 1.2 1.4
V/V_0
d
R
0.038
0.036
0.034
0.032
1.0 1.2 1.4
V/V_0
e
std(σ_{hyd}) (pN/nm^2)
15
10
5
0
1.0 1.2 1.4
V/V_0



python
Curvatures
geometry
Physics
geometry
Young's modulus
pressure
thickness
Geometry
graph
vertex coordinates
Graph
mesh
Sphere
radius
Spherocylinder
radius
length
EnergyMinimization
shell
conjugate gradient
energy
energy gradient
SciPy
conjugate gradient
energy
energy gradient
Stresses
shell
SpringModel
rest lengths
FiniteElementsModel
undeformed triangles
COMSOLInterface
shell
model
JPype
Java
COMSOL
Composition
Inheritance
Access


TensorBoard
TIME SERIES
SCALARS
DISTRIBUTIONS
HISTOGRAMS
INACTIVE
UPLOAD
Filter tags (regex)
All
Scalars
Image
Histogram
Settings
stretchingEnergy
stretchingEnergy
surfaceArea
surfaceArea
timePerIteration


TensorBoard
TIME SERIES
SCALARS
DISTRIBUTIONS
HISTOGRAMS
INACTIVE
UPLOAD
Point of view
Display all points
Current view
Share viewpoint
Runs
Write a regex to filter runs
9/cylinderGrowth_lin_strain_curvature_caps_degrowth
runs/2023-06-23-15_20_27/cylinderGrowth_hydrostatic_stress_offset
runs/2023-06-24-21_41_03/sphere_random_growth
runs/2023-06-24-22_04_44/cylinder_long_random_growth
runs/2023-06-24-22_48_52/sphere_random_growth
runs/2023-06-24-23_11_21/cylinder_long_random_growth
runs/2023-06-26-12_43_26/sphere_strain_based_rates_offset
runs/2023-06-26-14_39_03/sphere_strain_based_rates_exp
runs/2023-06-26-16_06_17/sphere_strain_based_rates
runs/2023-06-26-16_06_47/sphere_strain_based_rates
runs/2023-06-26-16_30_34/sphere_strain_based_rates
runs/2023-06-26-16_36_01/sphere_strain_based_rates
runs/2023-06-26-16_36_10/cylinderGrowth_random
TOGGLE ALL RUNS
/scratch/ge37buz/code/git/gerland_group/shell_growth
Filter tags (regular expressions supported)
mesh
step 186
Mon Jun 26 2023 20:37:12 GMT+0200 (Central European Summer Time)


energy
BendingEnergy
StretchingEnergy
PressureEnergy
energyGradient
BendingEnergyGradient
StretchingEnergyGradient
PressureEnergyGradient
EdgeLengths
TriangleNormalDotProducts
NormalVectors
Volumes
Areas
0
10000
20000
Execution times Numba jit (μs)
0
100
200
Execution times Cython (μs)
0
100
200
Advantage Cython over Numba