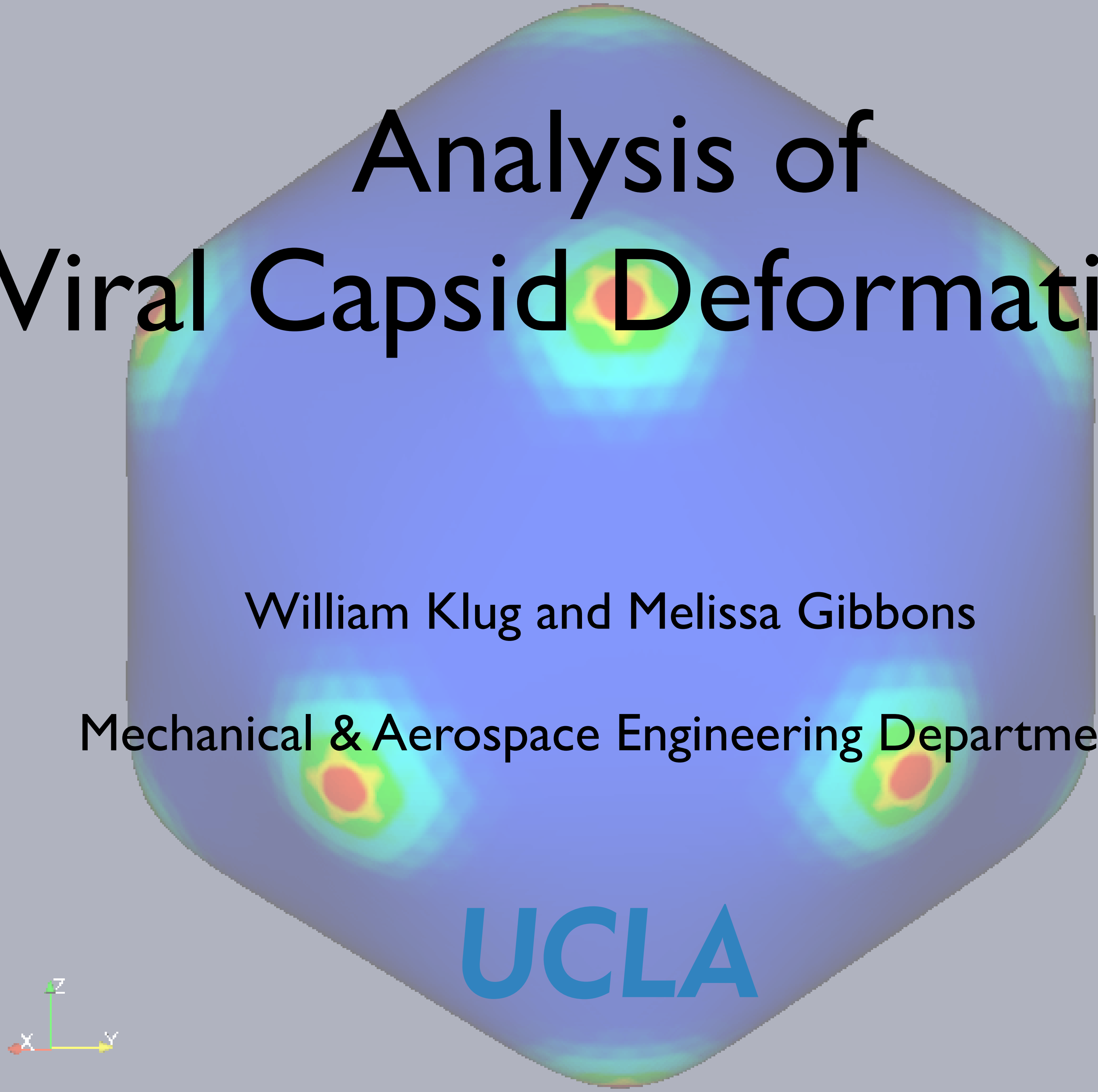
Analysis of Viral Capsid Deformation

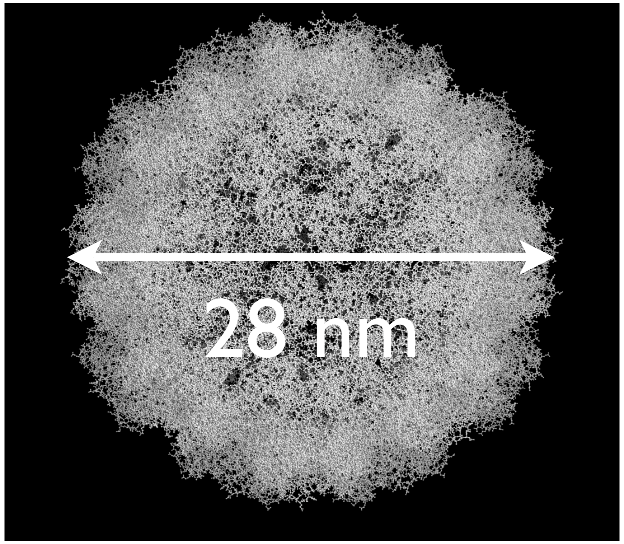


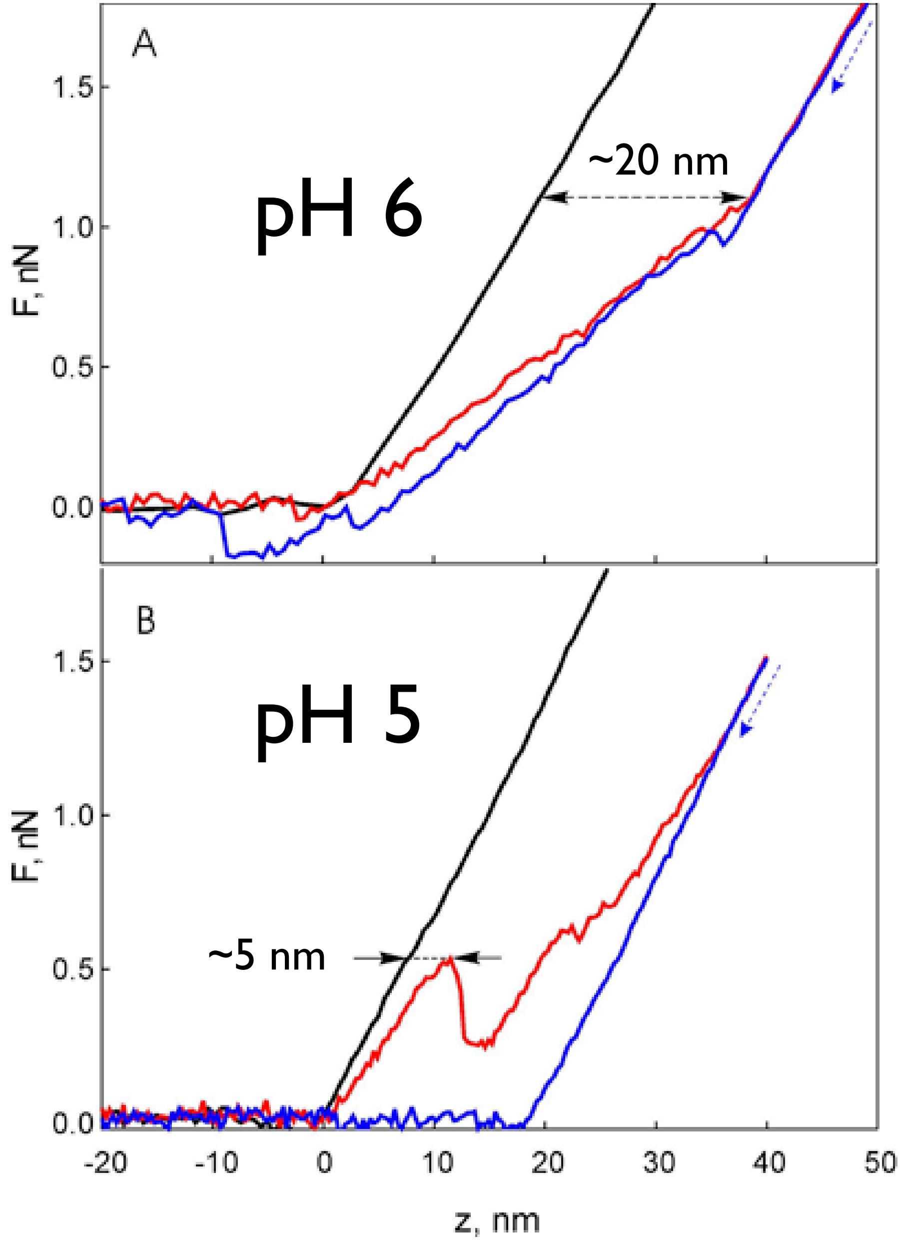
William Klug and Melissa Gibbons

Mechanical & Aerospace Engineering Department

UCLA

AFM mechanical testing of CCMV
(C. Knobler, et al.)





- Linearly elastic
  (even for large deformation)
- Slope changes with pH
- Irreversible damage at lower pH

Questions:

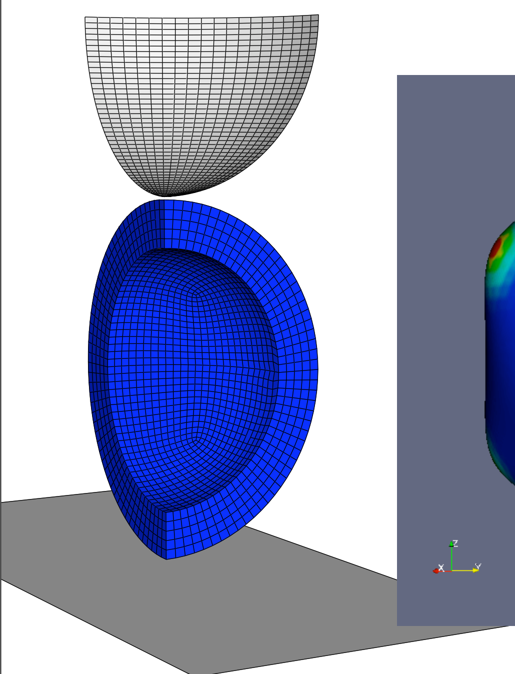
- Why is force response linear?
- What is responsible for damage?
- Why does damage occur only at lower pH?

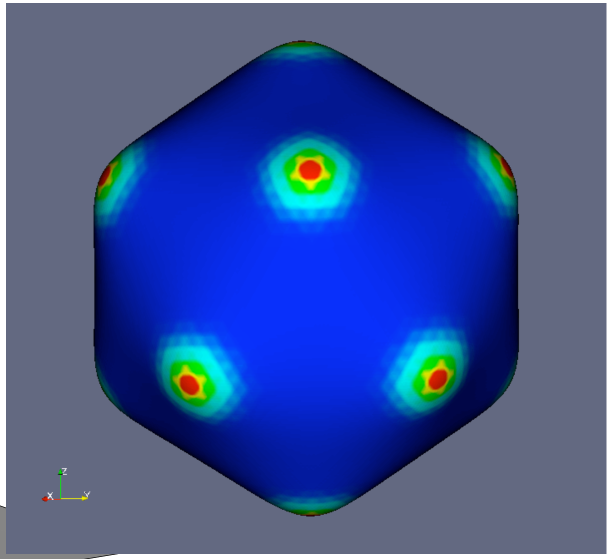
- Hypothesis: (nonlinear) elasticity has something to do with this.

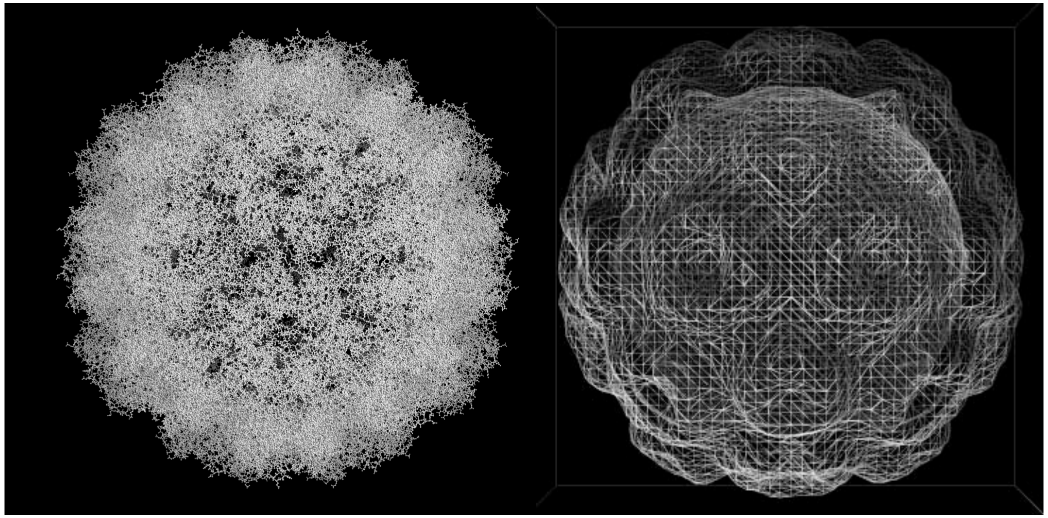
The Strategy: coarse-grain

Throw away as many DOF as possible while retaining a model which has the right Physics (and Biology?).

- Continuum elasticity in 3-D and 2-D
- Multi-scale simulation







3-D Continuum Model: Thick Spherical Shell

After all, aren't capsids more spherical than horses?

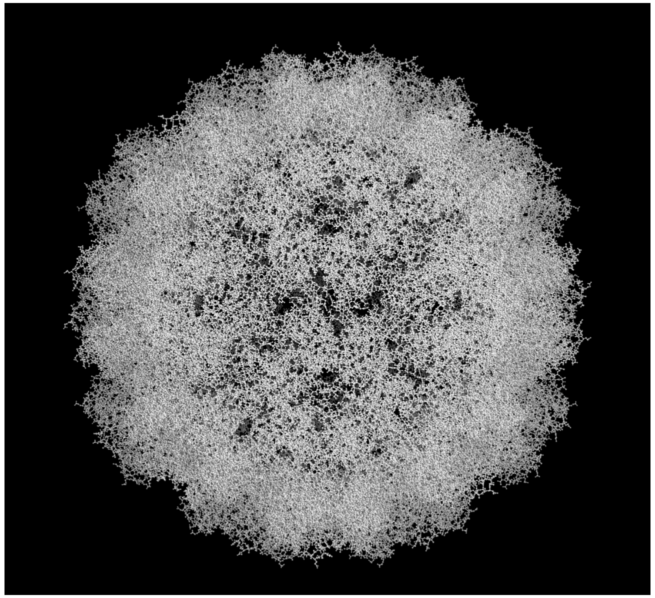
$$\mathcal{H} = \int_V w(E_{ij})\,dV - W^{\text{ext}}$$

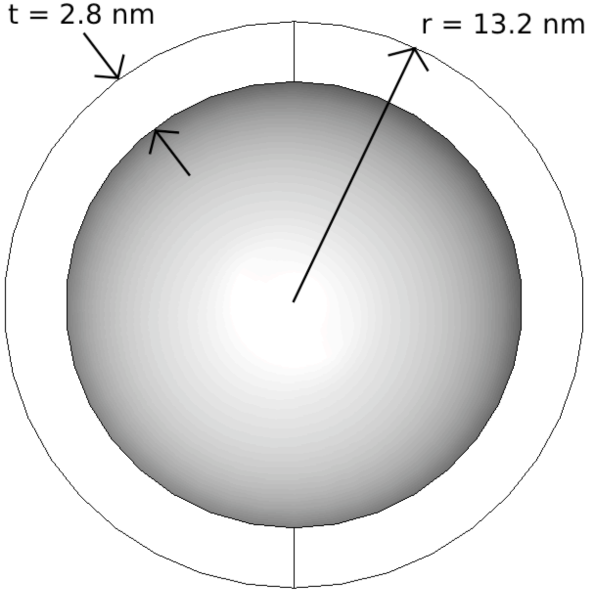
$$\mathbf{E} = \frac{1}{2}\left(\nabla\vec{u} + \nabla\vec{u}^{\mathsf{T}} + \nabla\vec{u}^{\mathsf{T}}\nabla\vec{u}\right)$$

$\vec{u}$ = displacement field

W^{ext} = work of external forces

$$\boldsymbol{\sigma} = \frac{\partial w}{\partial \mathbf{E}} = \text{stress tensor}$$





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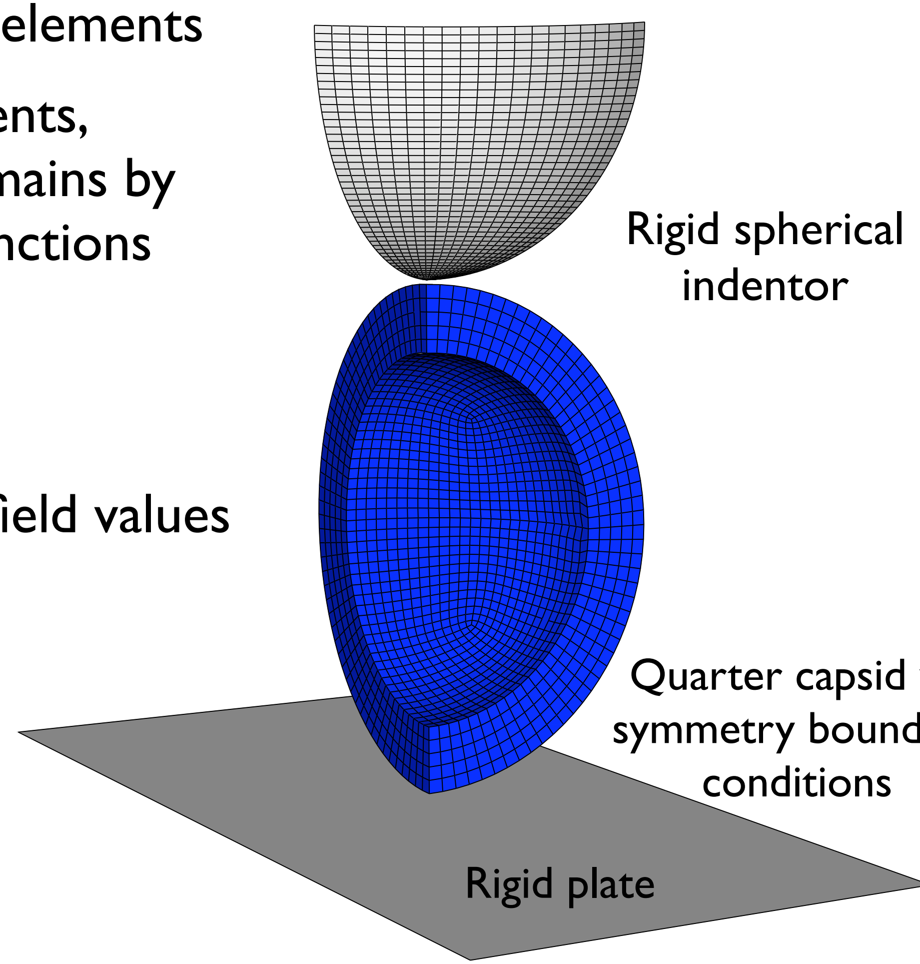
The Finite Element Method (FEM)

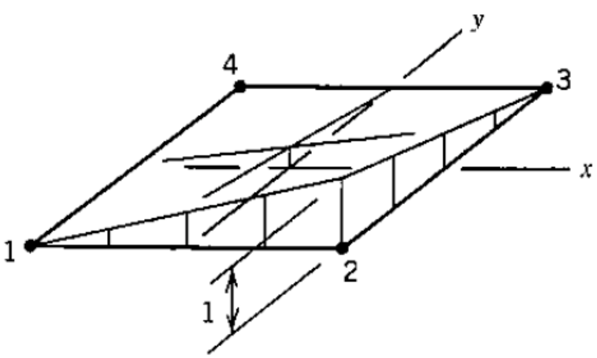
- Discretize shape into simple polyhedral elements
- Approximate unknown field (displacements, deformed shape) locally on element domains by interpolation simple polynomial basis functions

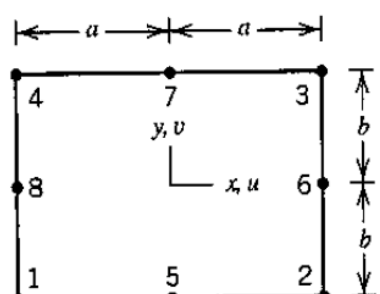
$$\vec{u}(\vec{r}) = \sum_{a=1}^{N} \vec{u}_a N_a(\vec{r})$$

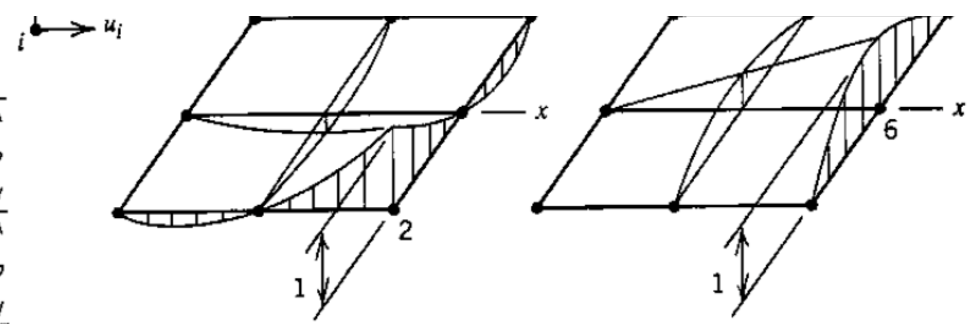
- Minimize energy with respect to nodal field values (Ritz Method)

$$\min_{\{\vec{u}_a\} \in \mathbb{R}^{3N}} \mathcal{H}$$









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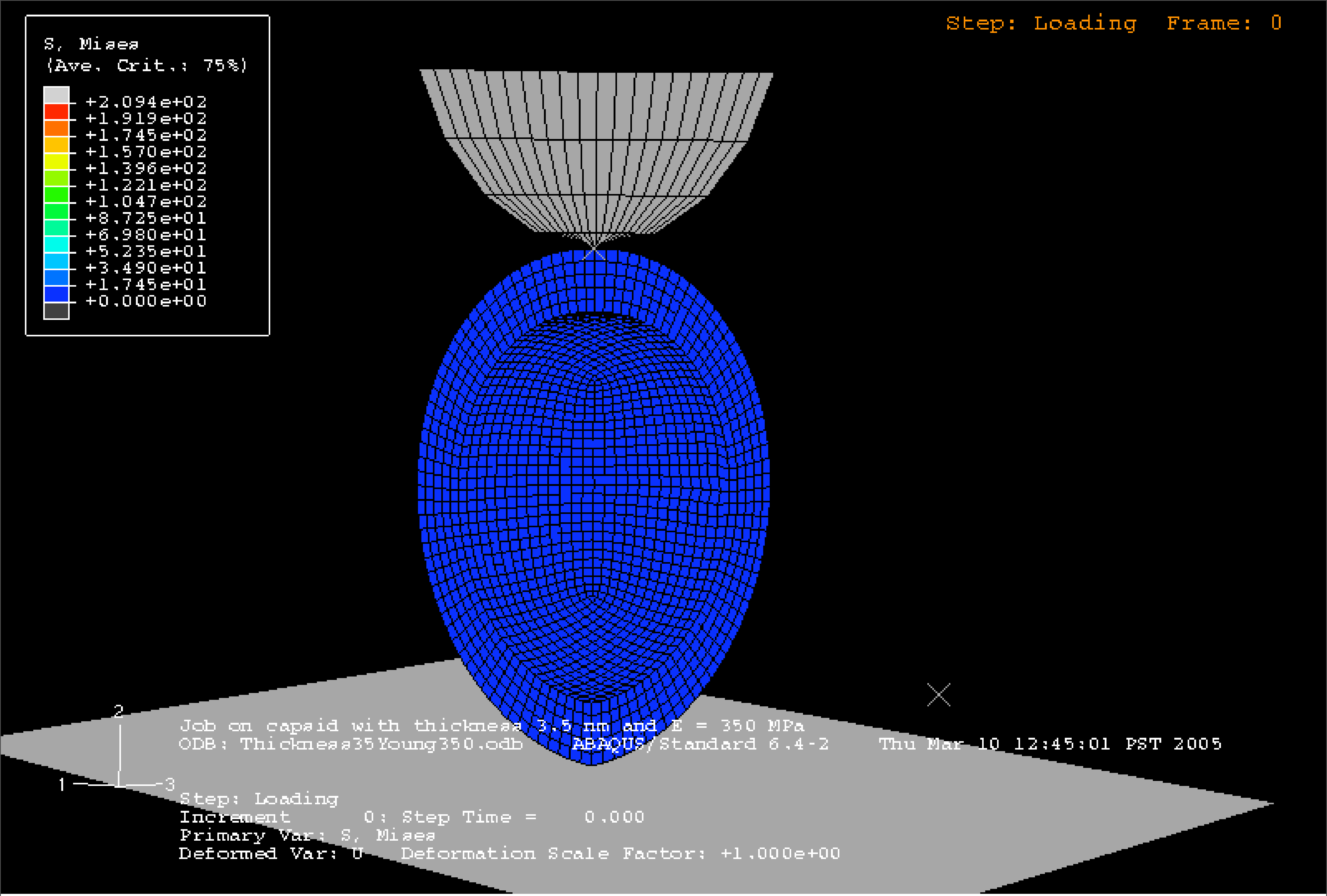
Melissa Gibbons' simulation



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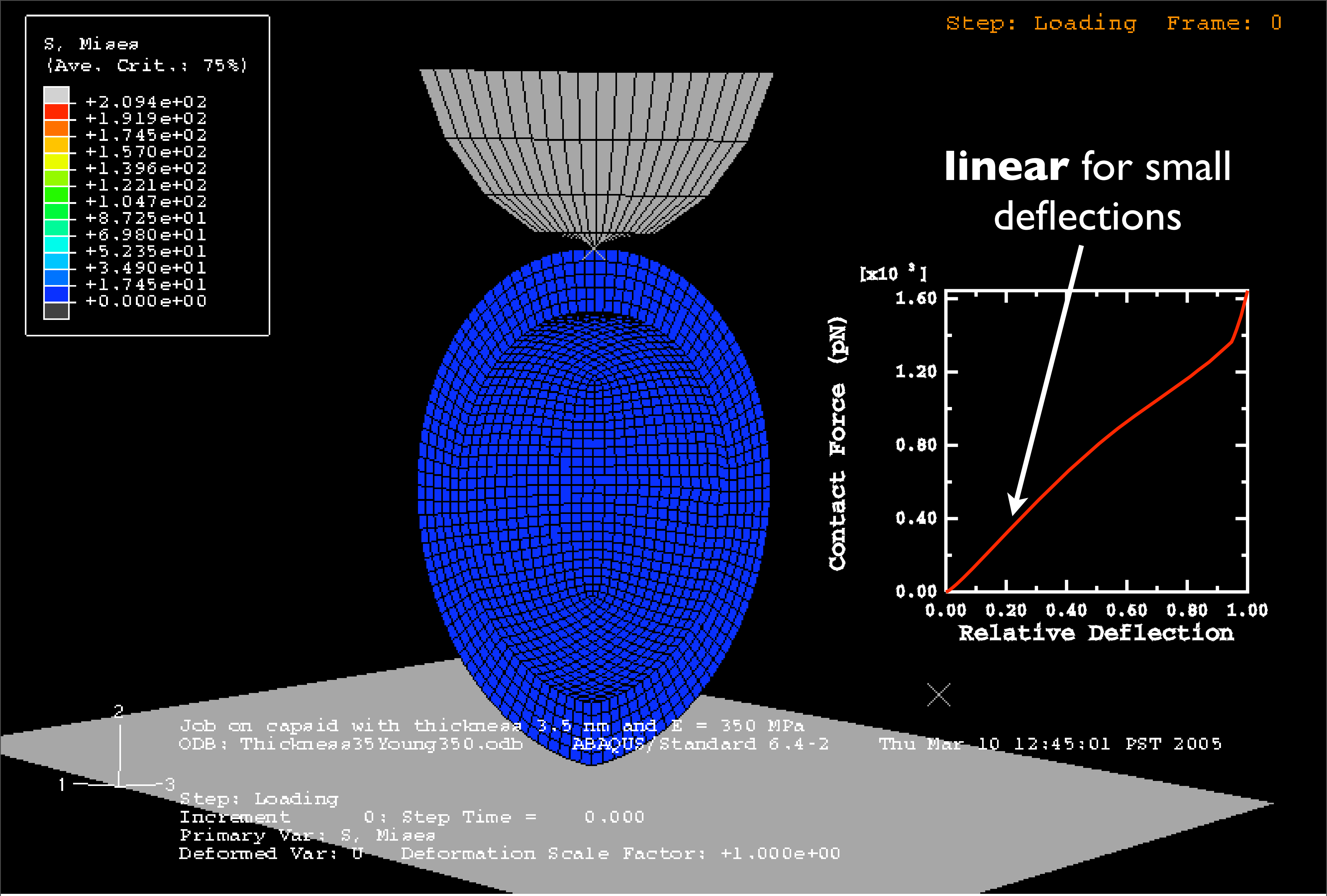
Melissa Gibbons' simulation



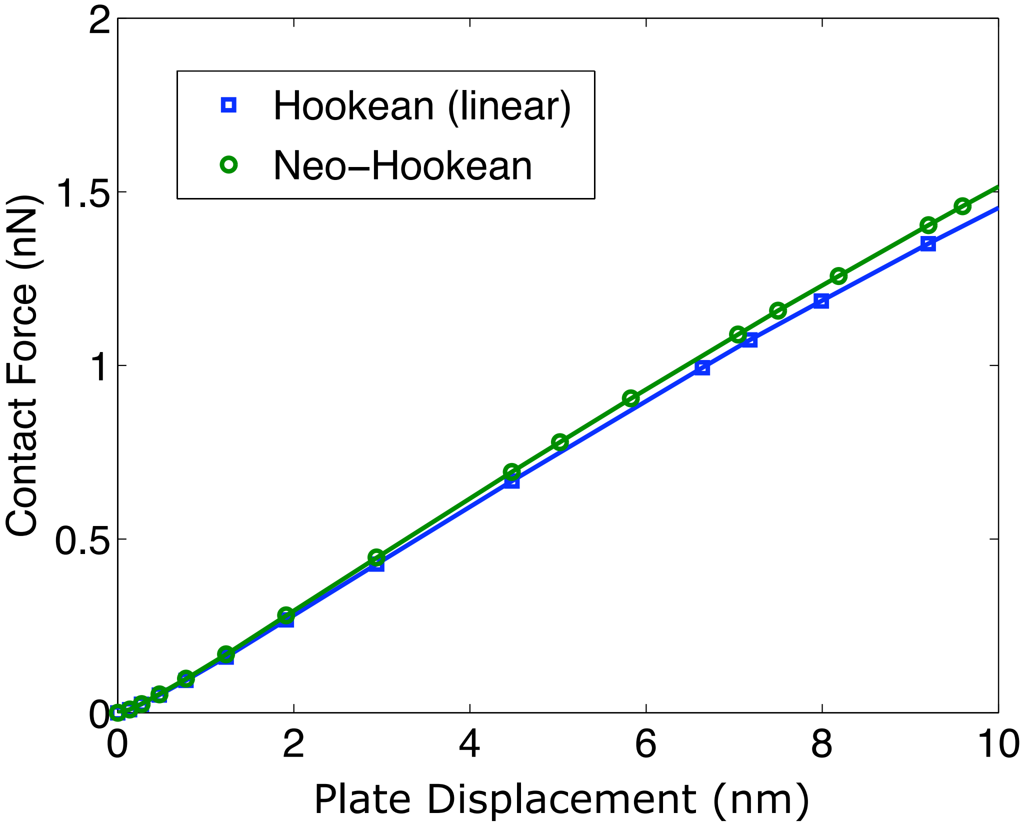
Melissa Gibbons' simulation

Constitutive models

- (Linear) Hookean:

$$w = \frac{\lambda}{2}(\mathrm{tr}\,\mathbf{E})^2 + \mu(\mathrm{tr}\,\mathbf{E}^2)$$

$$\boldsymbol{\sigma} = \lambda(\mathrm{tr}\,\mathbf{E})\mathbf{1} + 2\mu\mathbf{E}$$



- Compressible Neo-Hookean (rubber elasticity):

$$w = \frac{1}{2}\lambda_0(\ln J)^2 - \mu_0 \ln J + \frac{\mu_0}{2}(\mathrm{tr}\,\mathbf{C} - 3)$$

$$\mathbf{C} = 2\mathbf{E} + \mathbf{1} \qquad J = (\det \mathbf{C})^{1/2}$$

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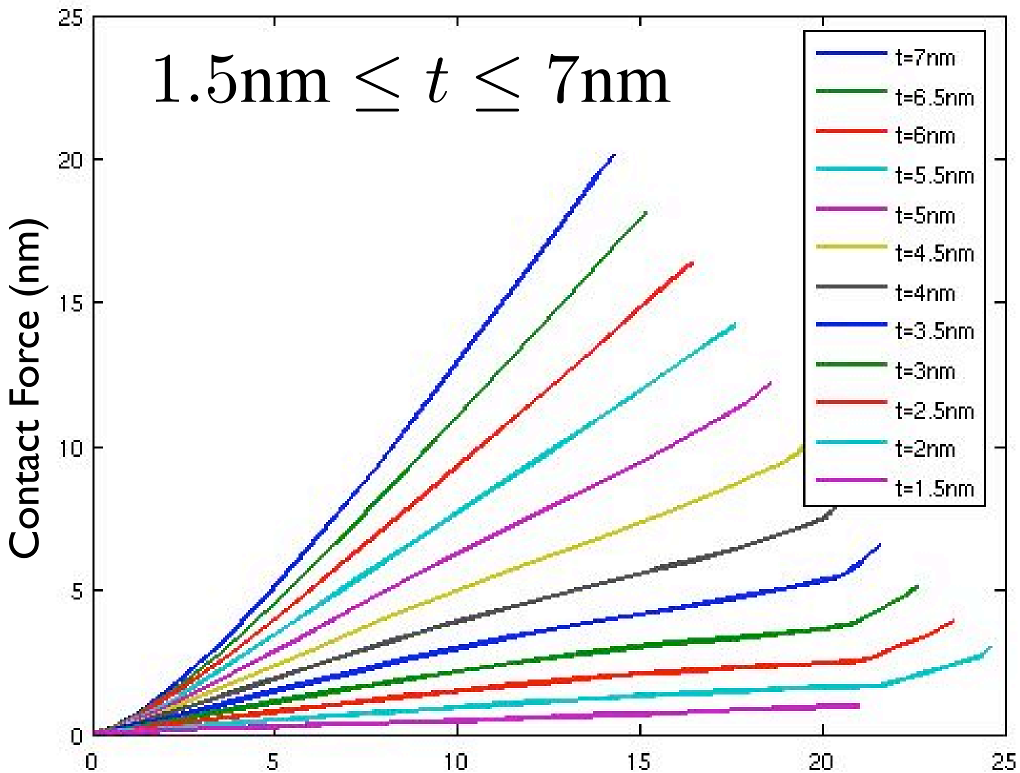
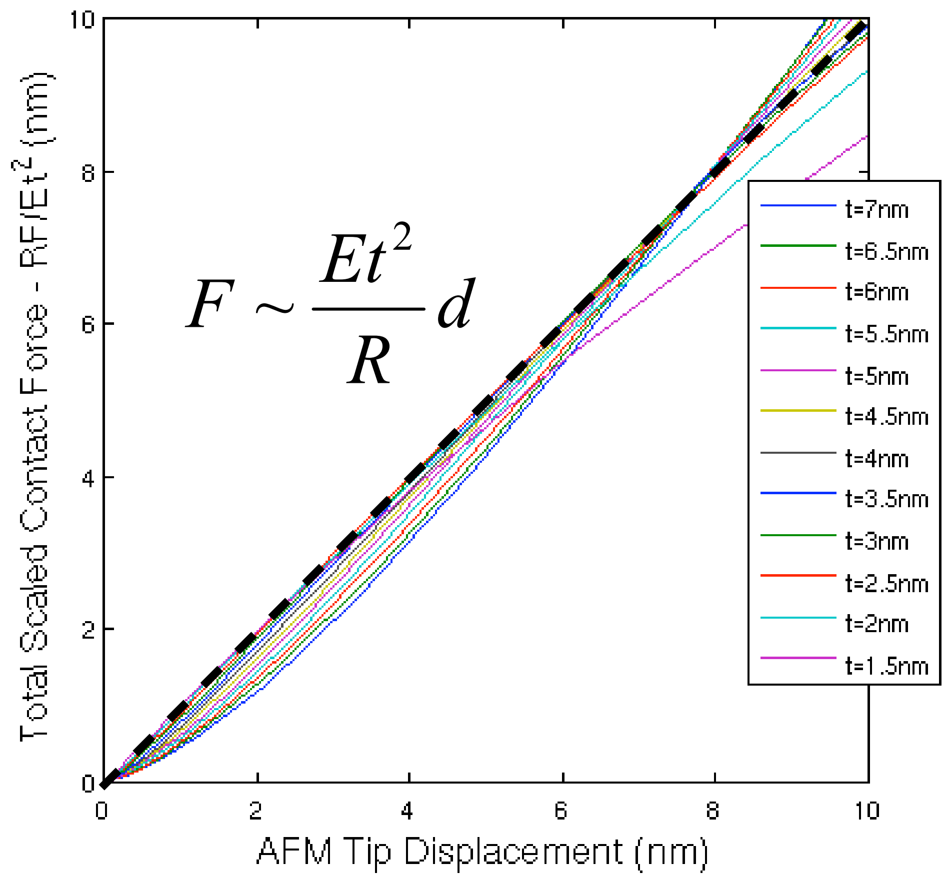
Thickness Variation





"Most" linear at $t \approx 3\text{nm}$ (average physical thickness)

Fit to experiment: $E \approx 250\text{MPa}$

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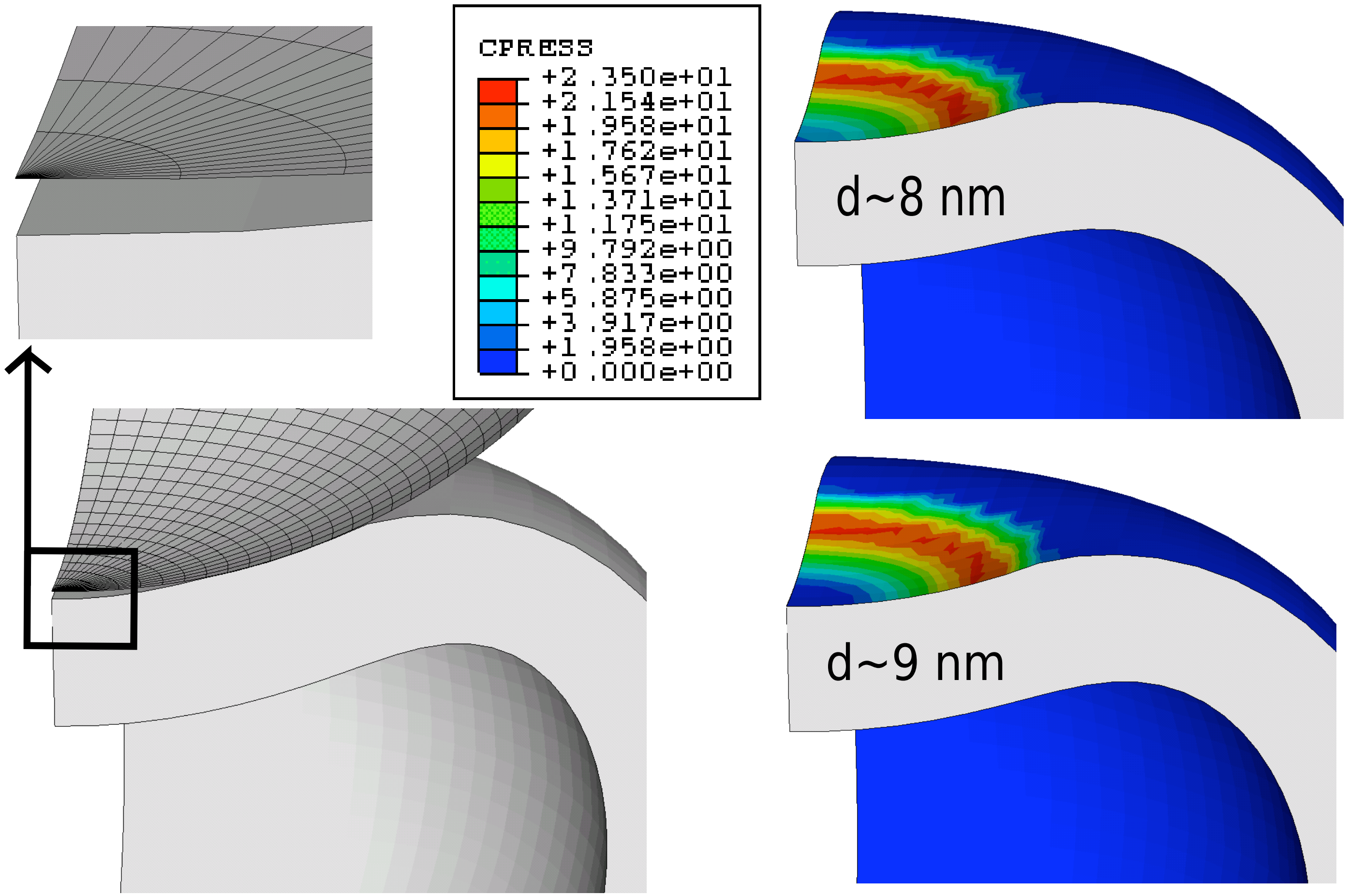
“Buckling”-type separation from tip



(a) Capsid Buckling, d~12 nm (b) Contact Pressure

Separation is associated with a softening of force response

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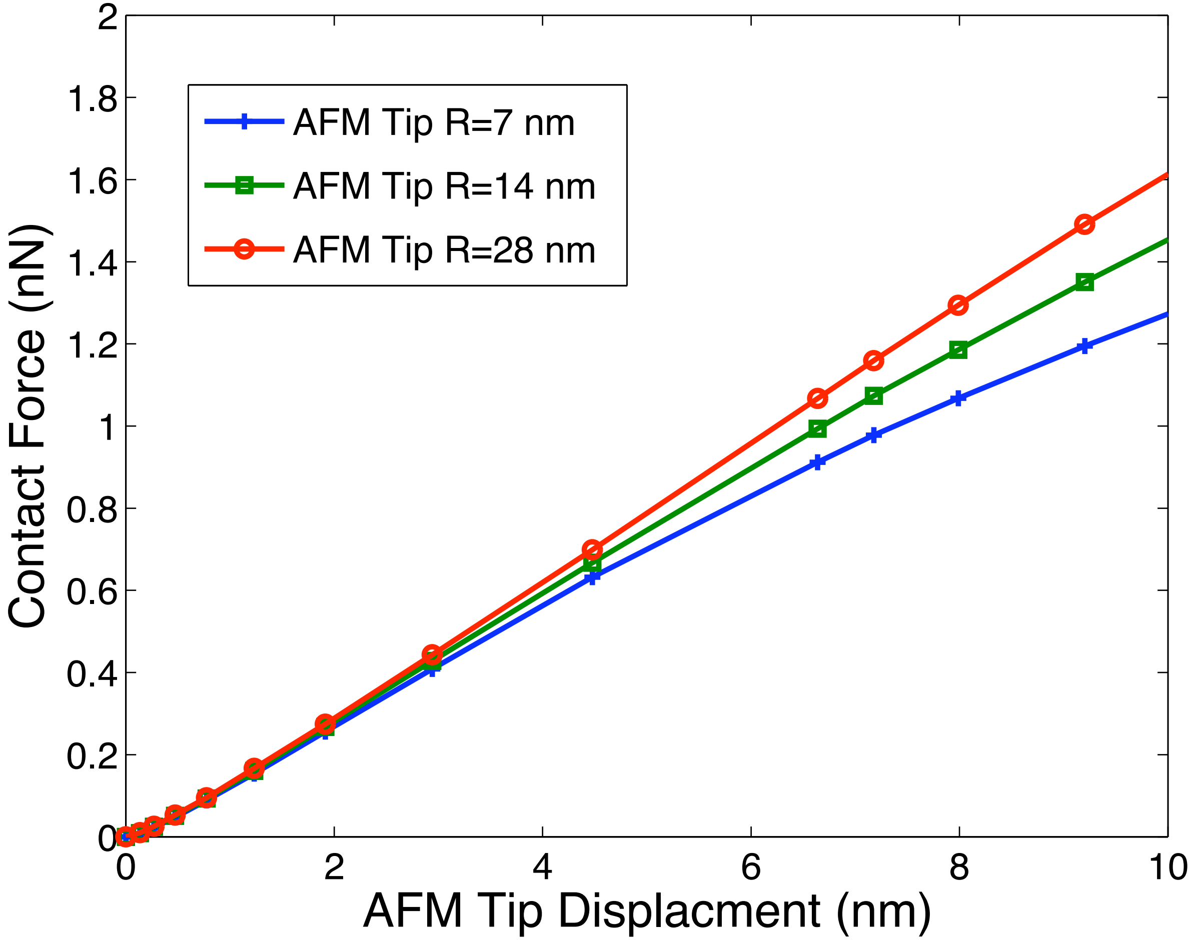
Insensitivity to Tip-size



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Lessons from 3-D models

- Thickness affects linearity
- Results insensitive to tip size, constitutive model
- Signs of buckling observed
- No explanation of failure

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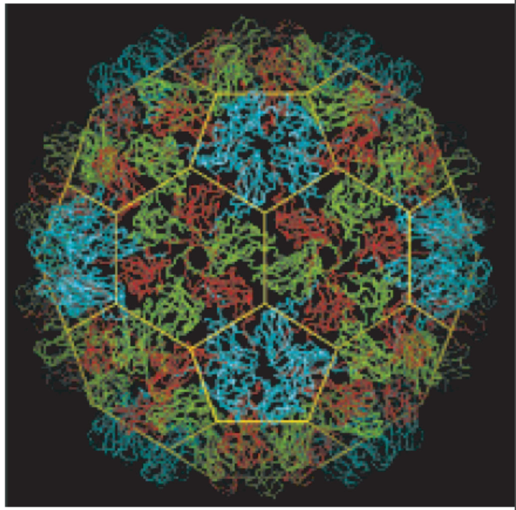
2-D Continuum Model: Thin Icosahedral Shell

considering structural symmetries



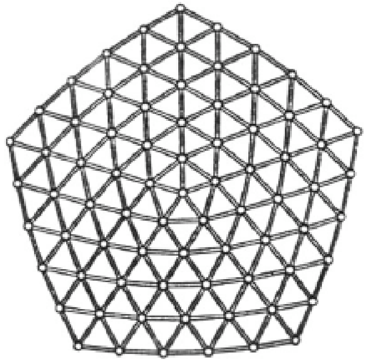
- Lidmar, Mirny, Nelson, PRE (2003)
  - Energy is a balance of bending and stretching

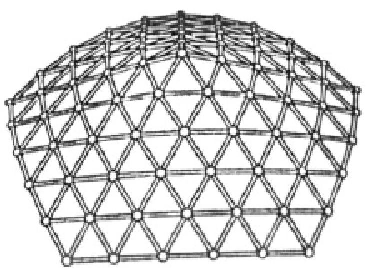
$$\mathcal{H} = \frac{\kappa}{2}\int H^2 dA + \frac{1}{2}\int (\lambda E_{ii}^2 + 2\mu E_{ij}E_{ij})dA - W^{\rm ext}$$

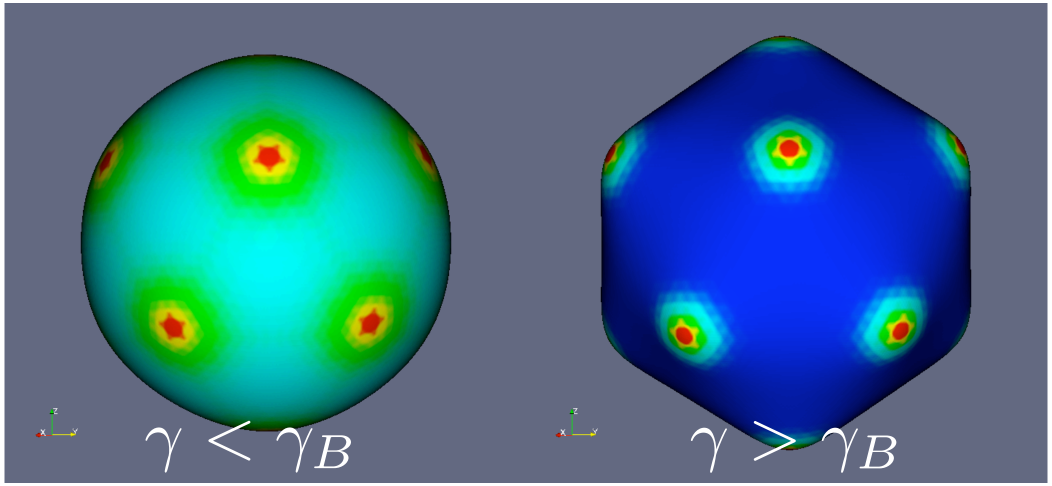
  - Faceting controlled by Föppl - von Kármán number

$$\gamma = \frac{YR^2}{\kappa} \qquad Y = \frac{4\mu(\mu+\lambda)}{2\mu+\lambda}$$

  - 5-fold sites are Disclinations







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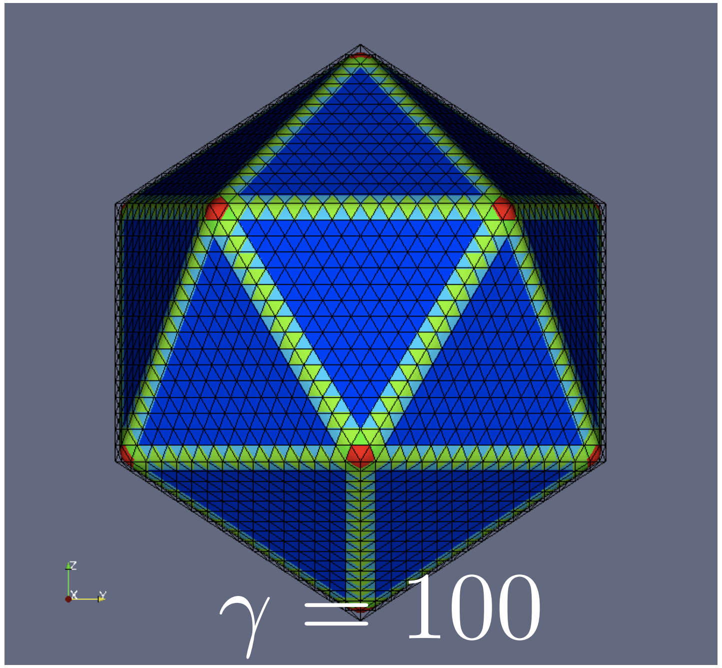
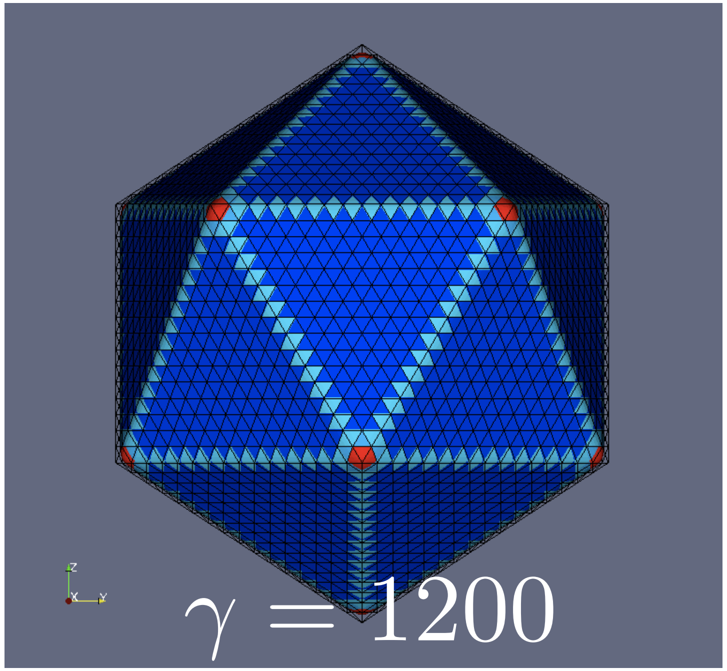
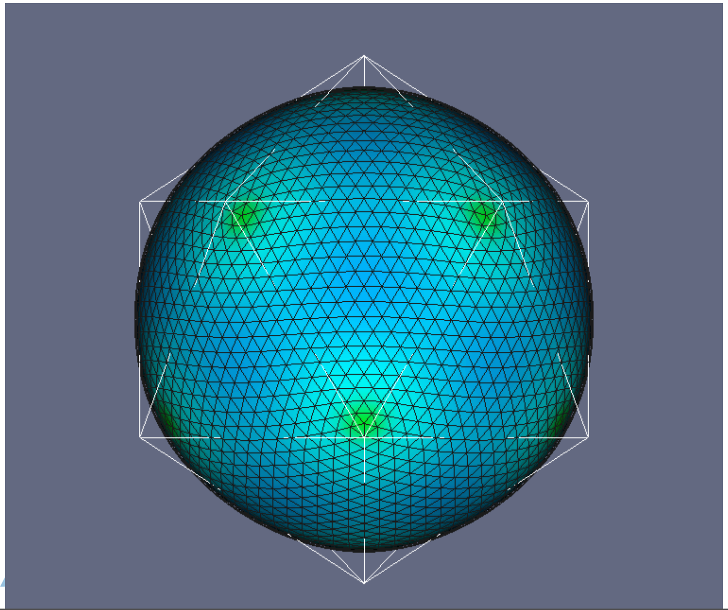
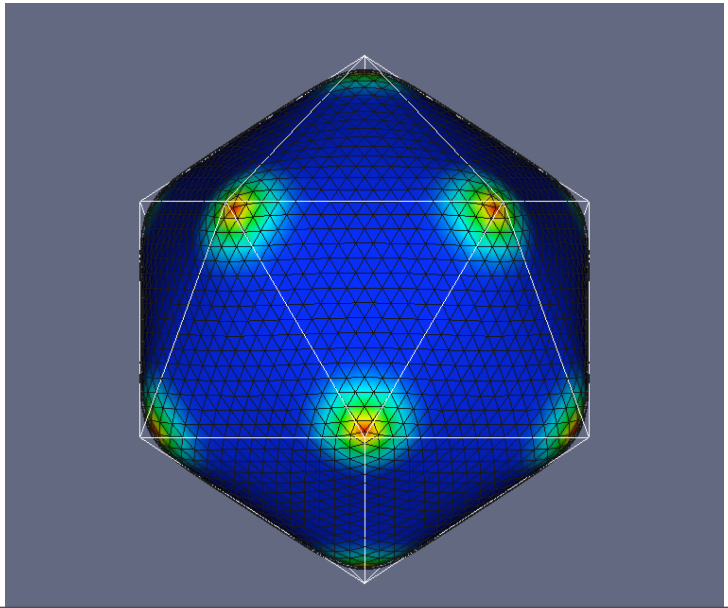
Thin-shell Finite Elements

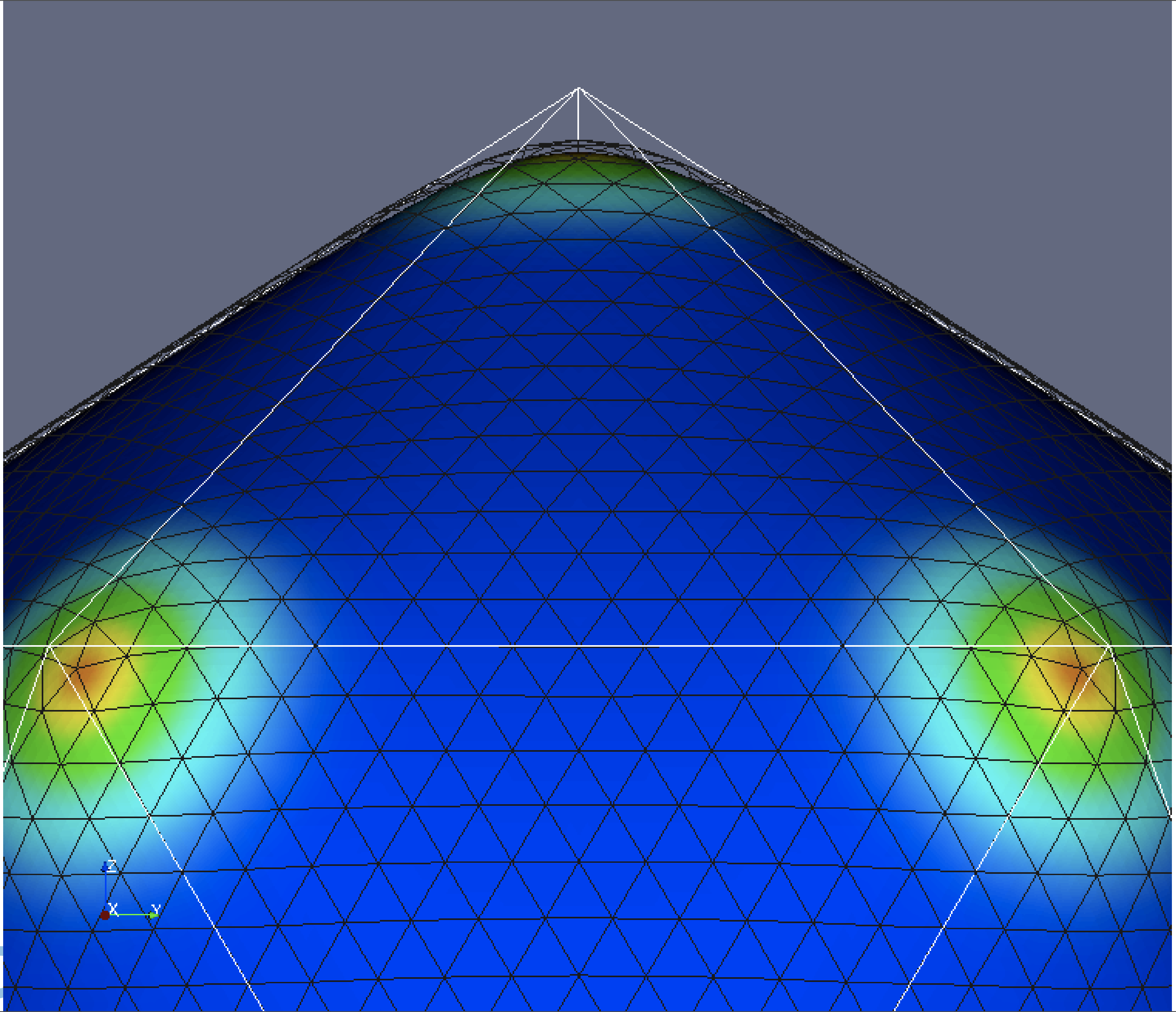
2562 vertex (T=256) mesh



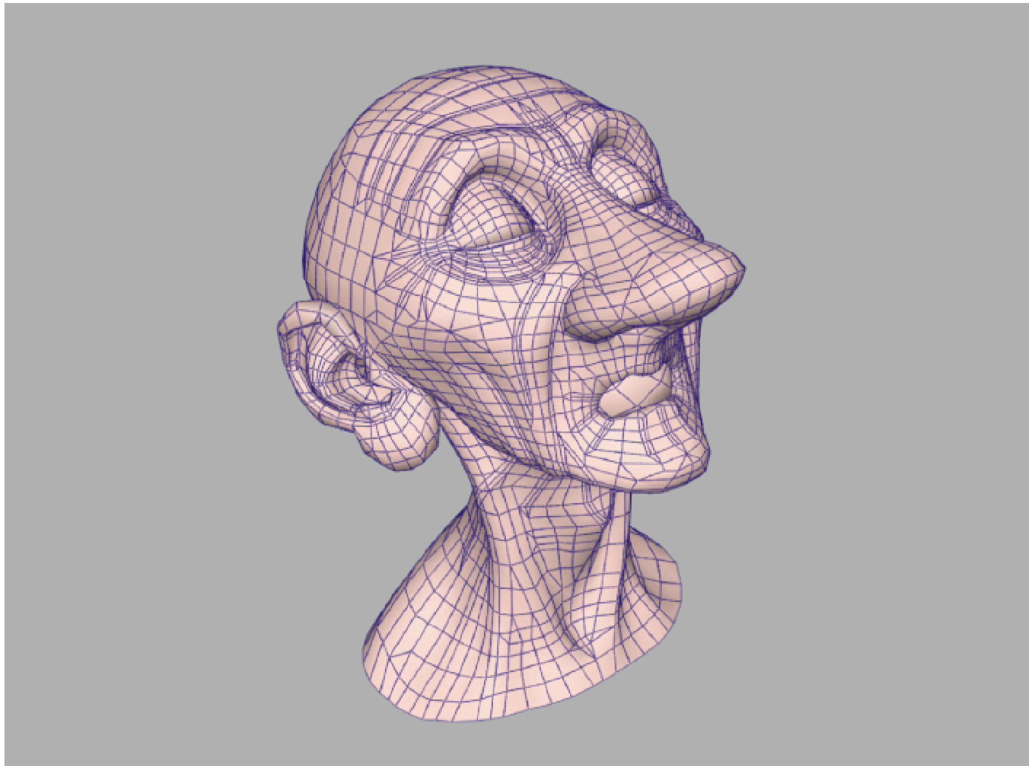


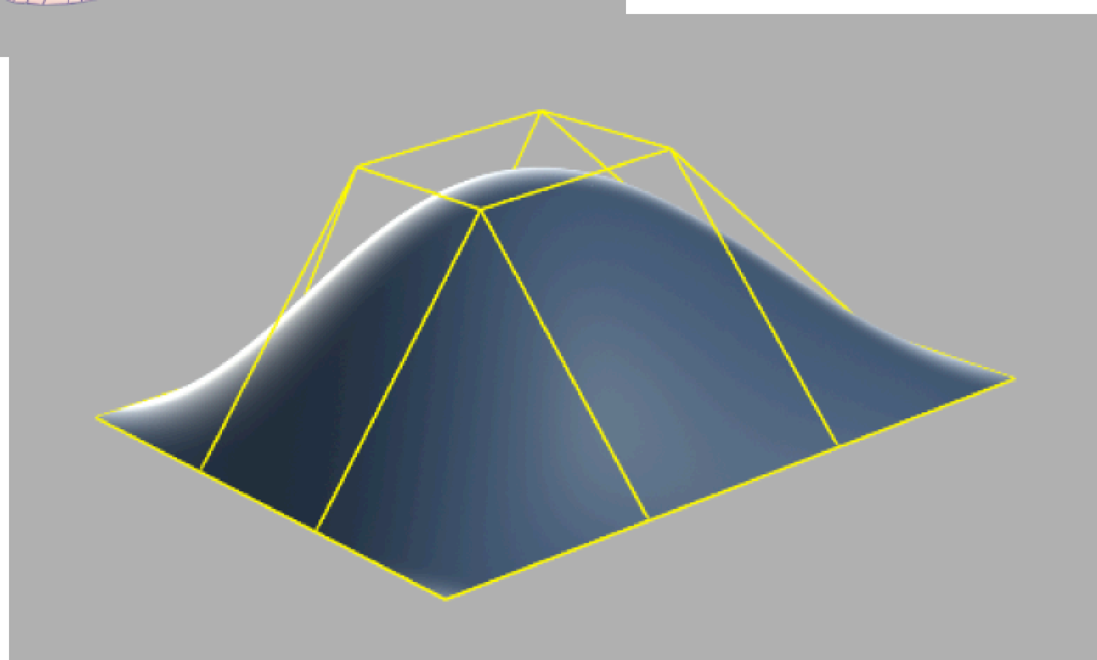





z
x
y

Local Polynomial Approximation





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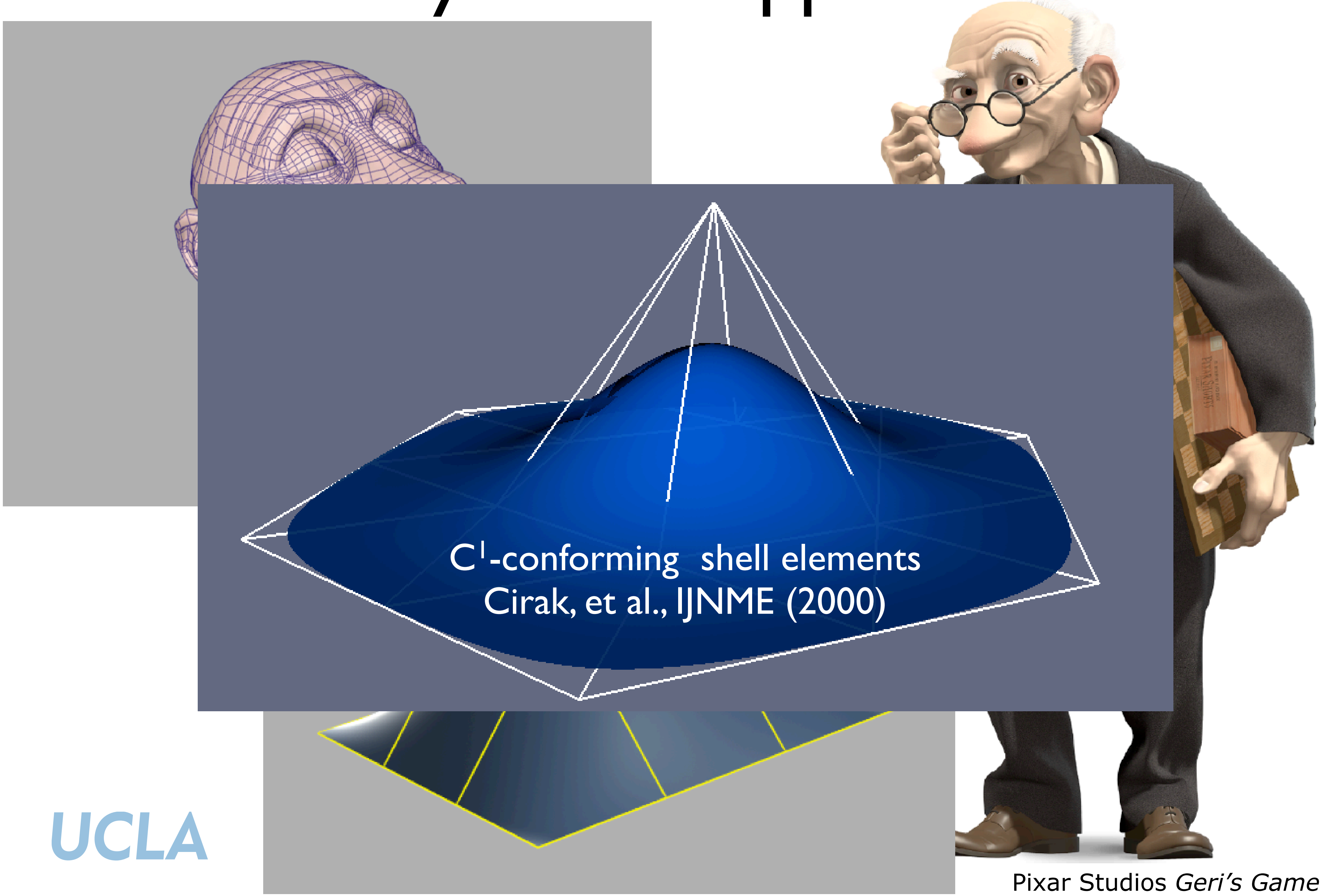
Pixar Studios *Geri's Game*

Local Polynomial Approximation



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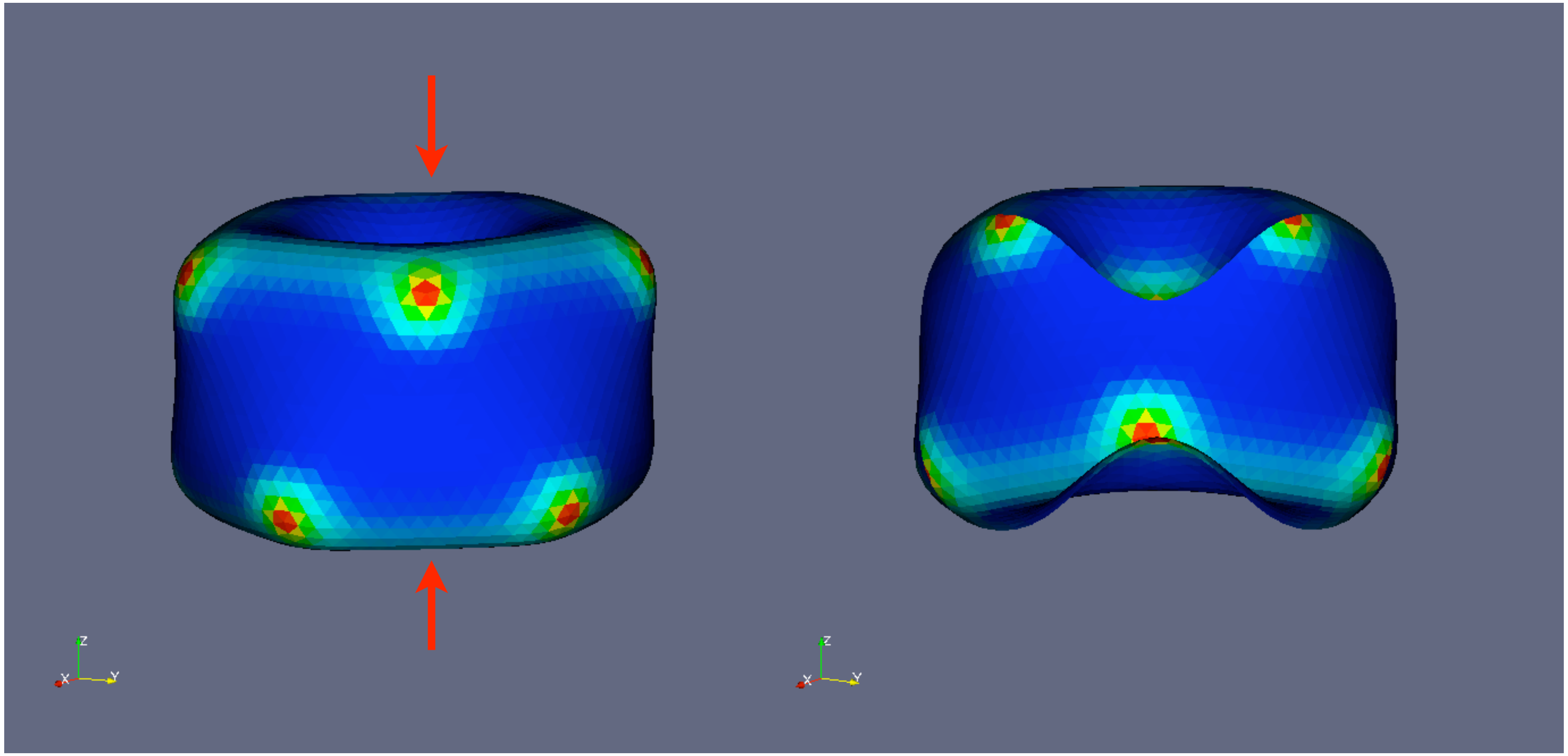
Pixar Studios *Geri's Game*

Icosahedral imperfections facilitate Buckling



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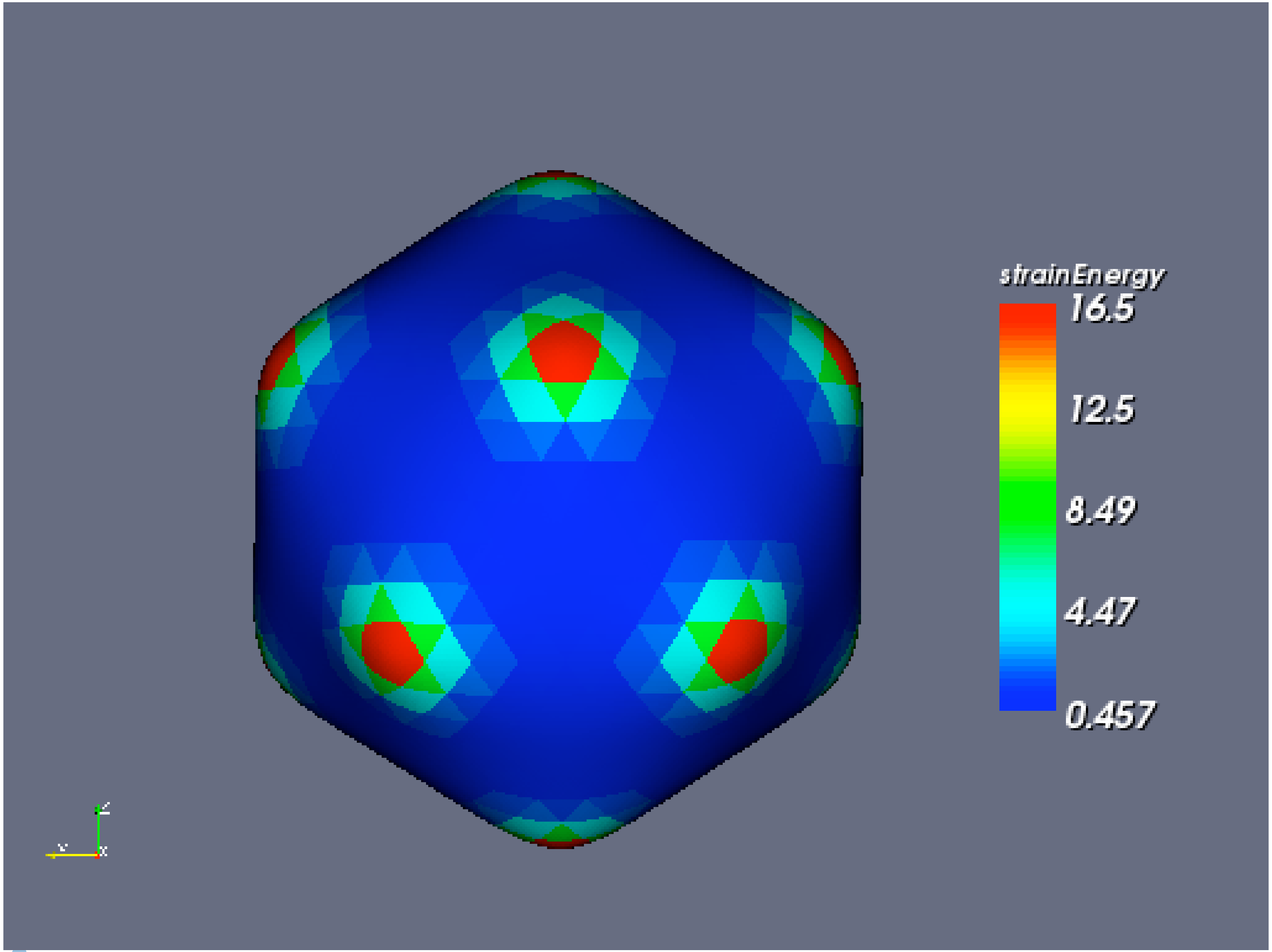
Icosahedral imperfections facilitate Buckling



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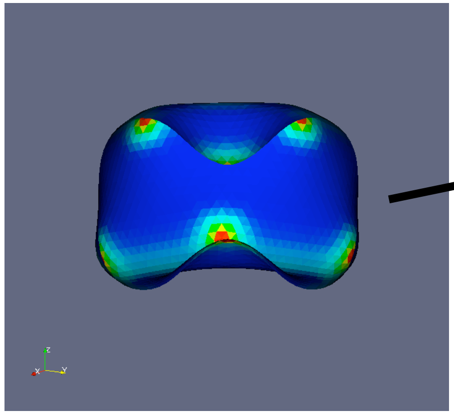
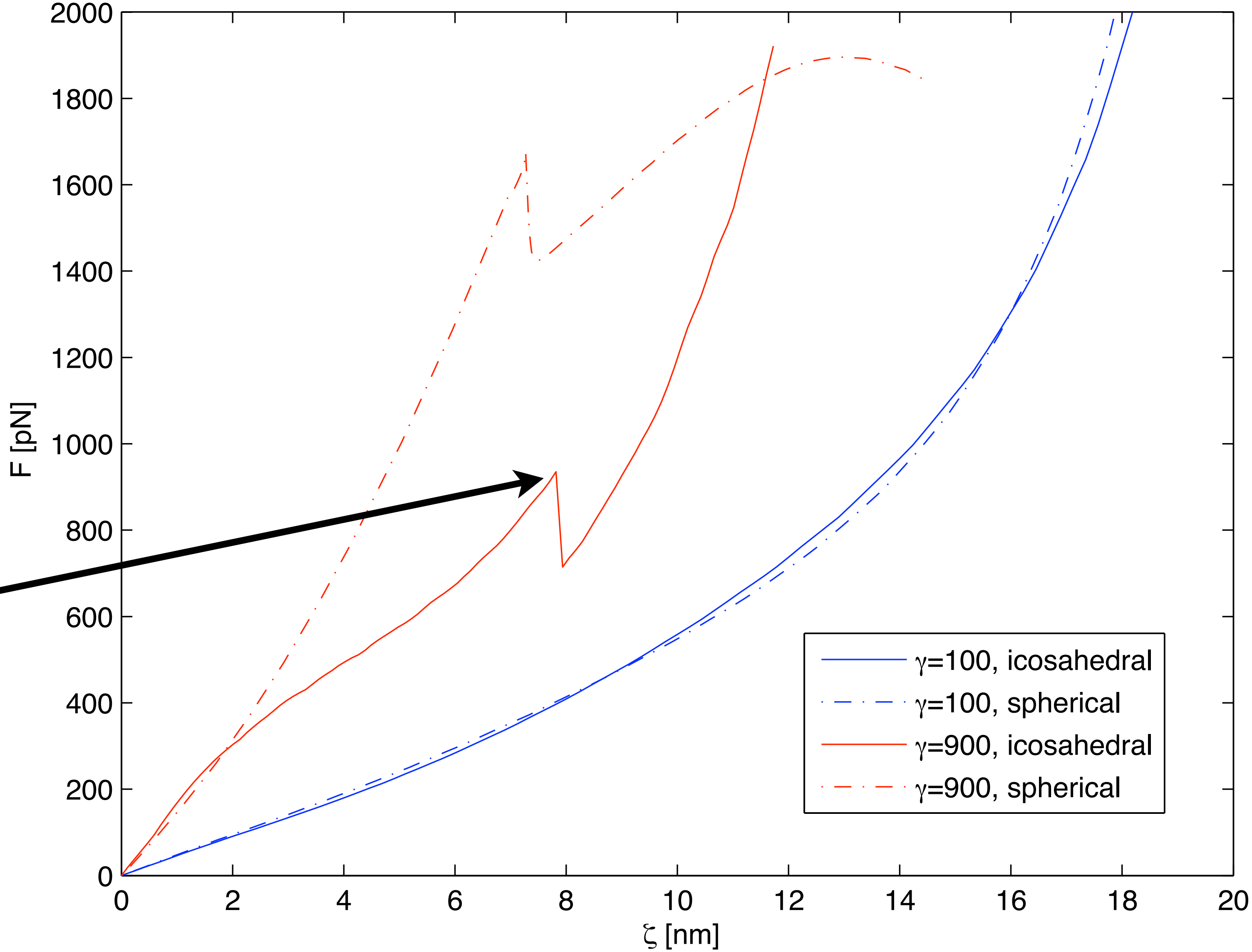
Icosahedral imperfections facilitate Buckling

shells compressed
between two flat plates
along 5-fold axis





Dashed lines: ref. state is spherical

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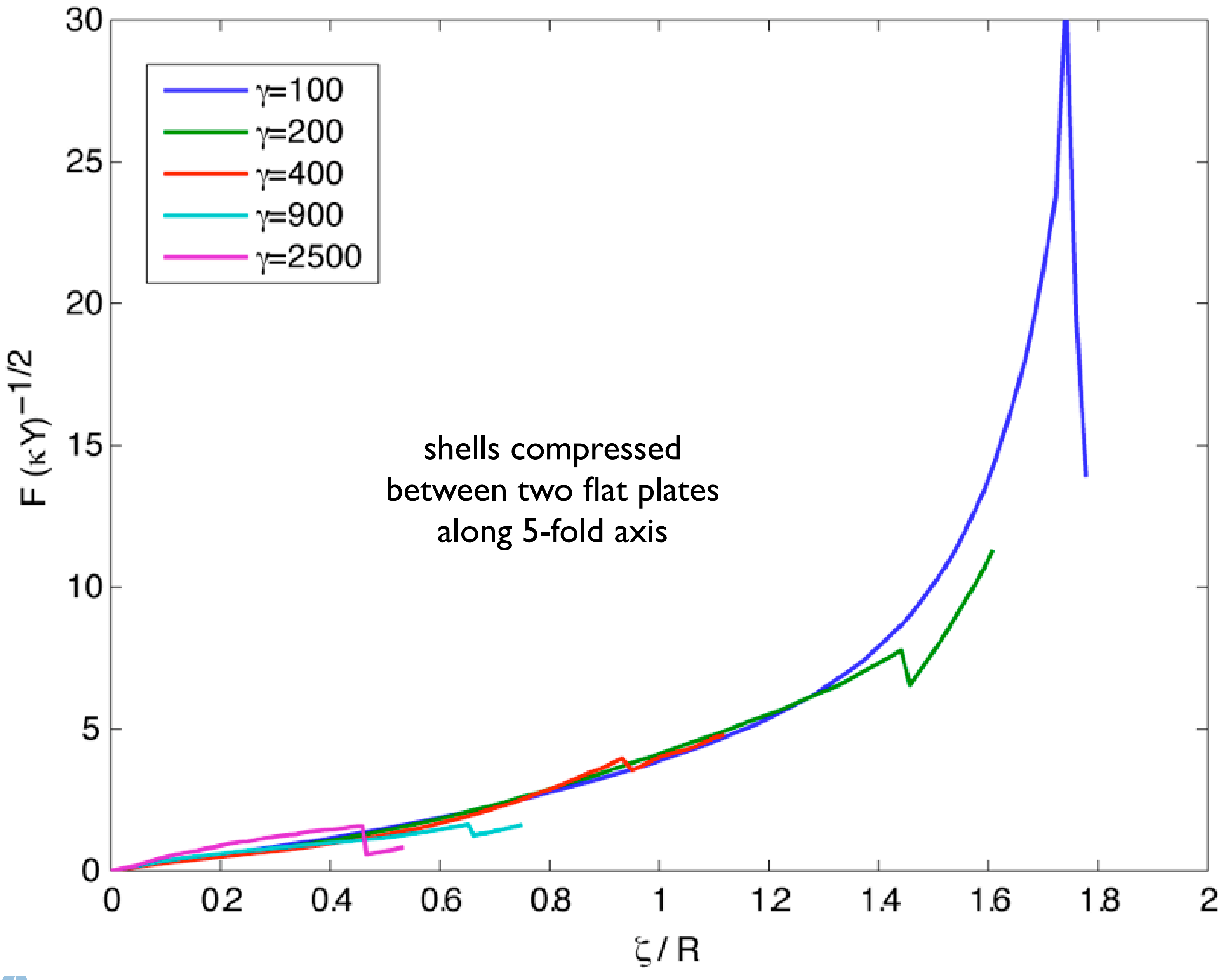
Scaled Force-deflection response vs FvK number



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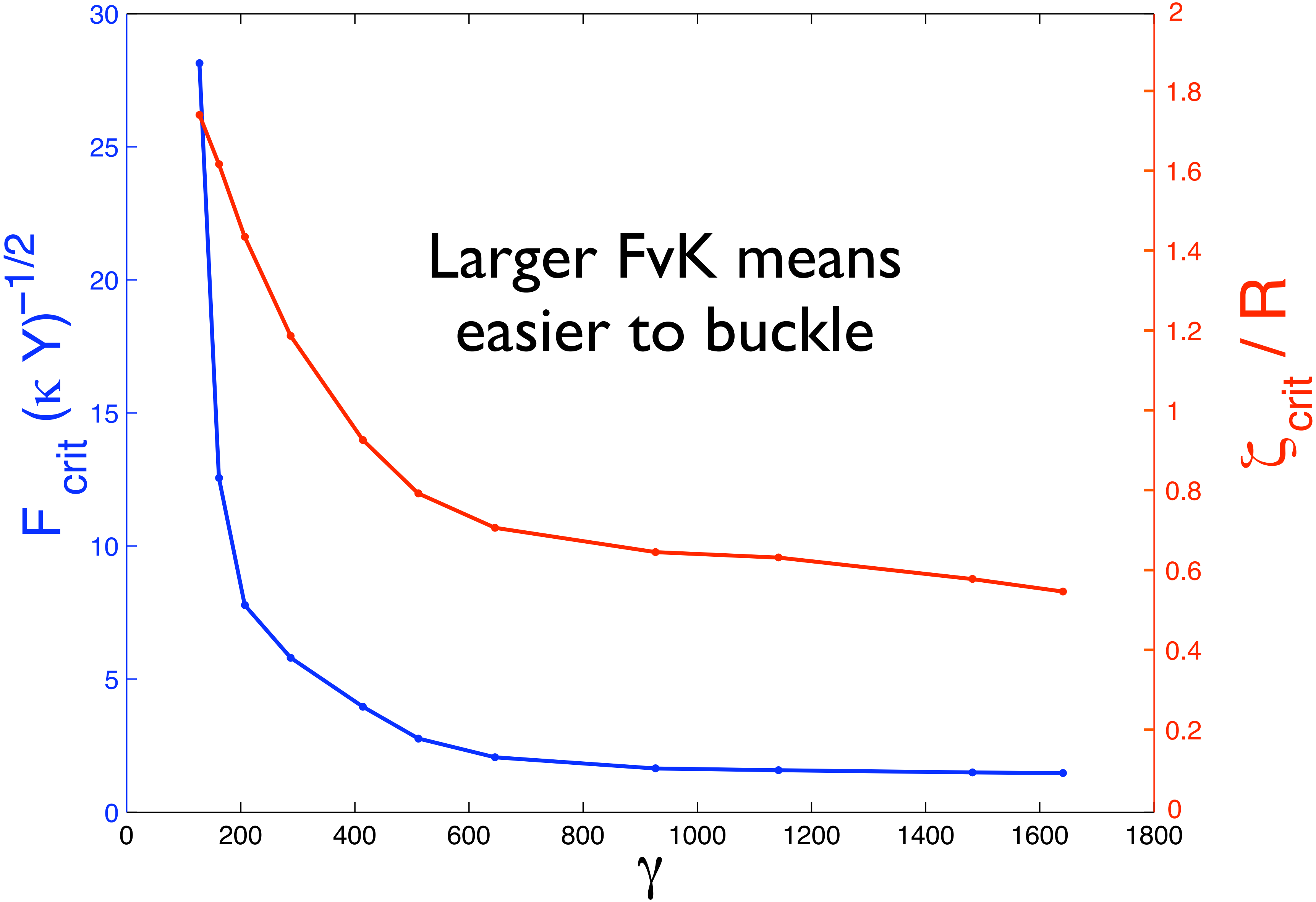
Critical force and deflection vs FvK number



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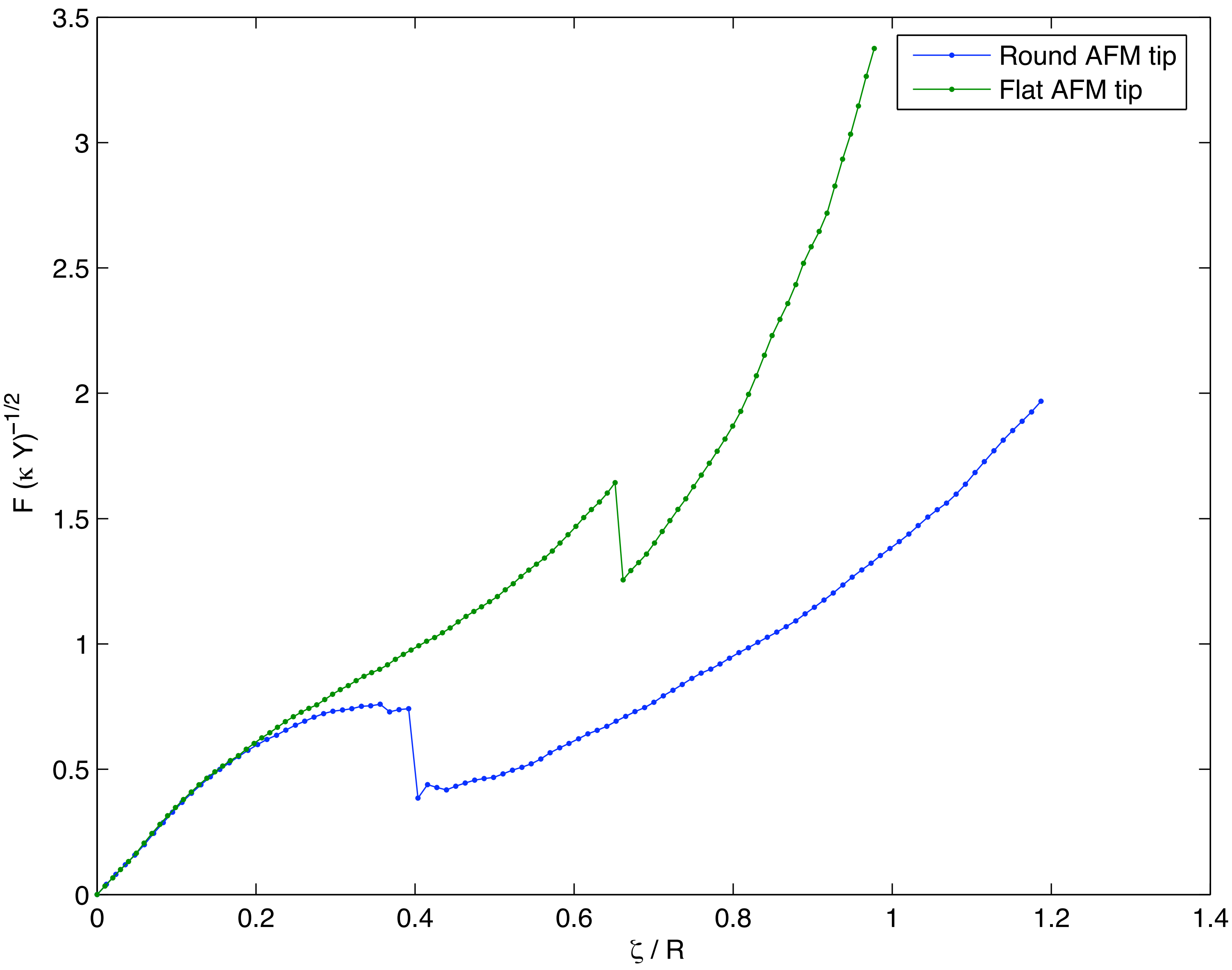
Influence of Tip Shape



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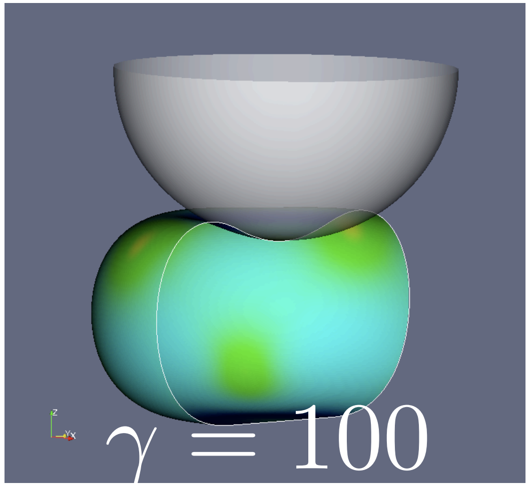
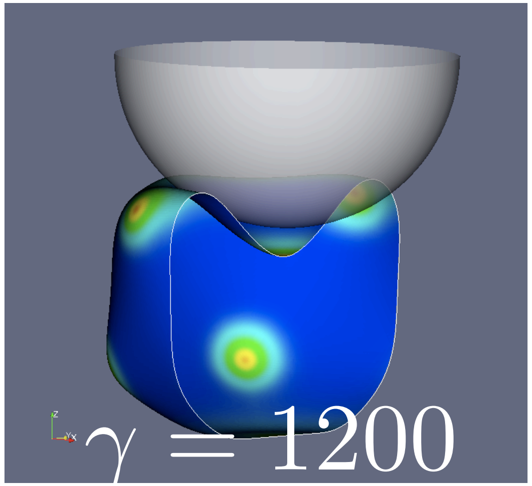
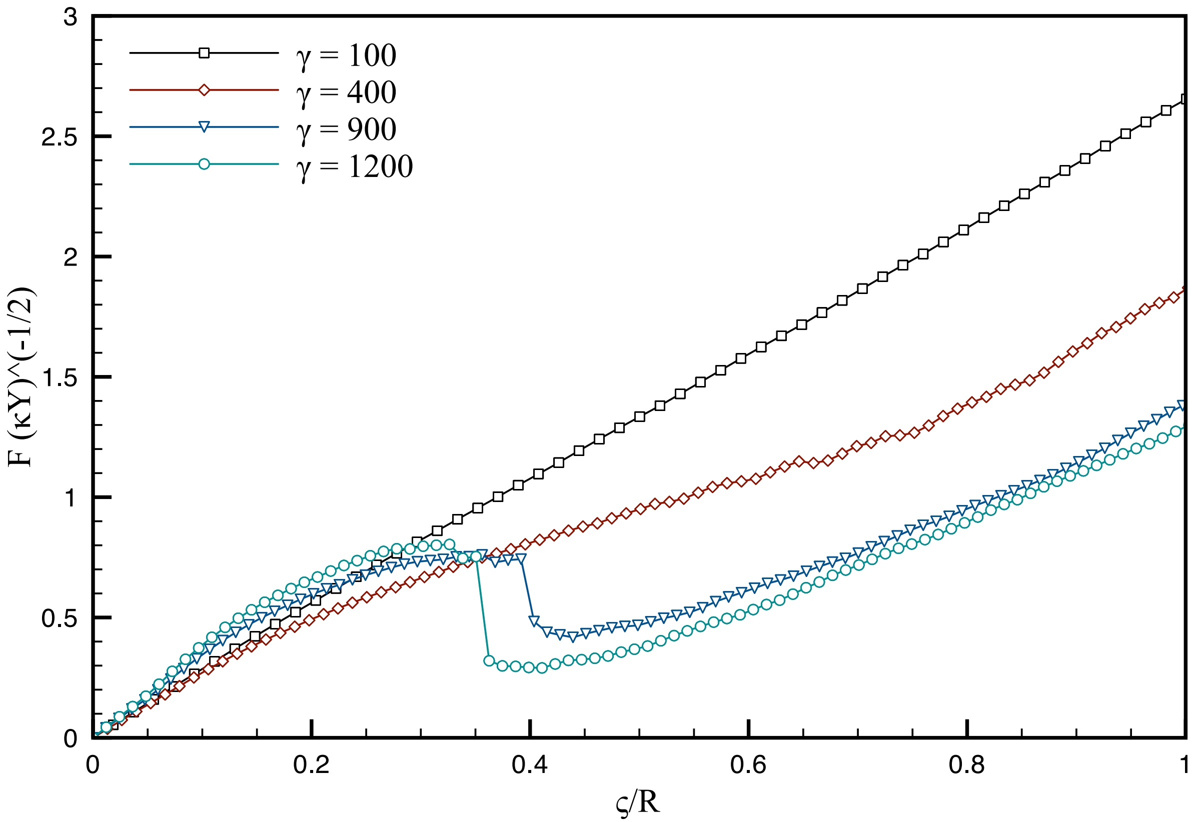
Simulating AFM experiments







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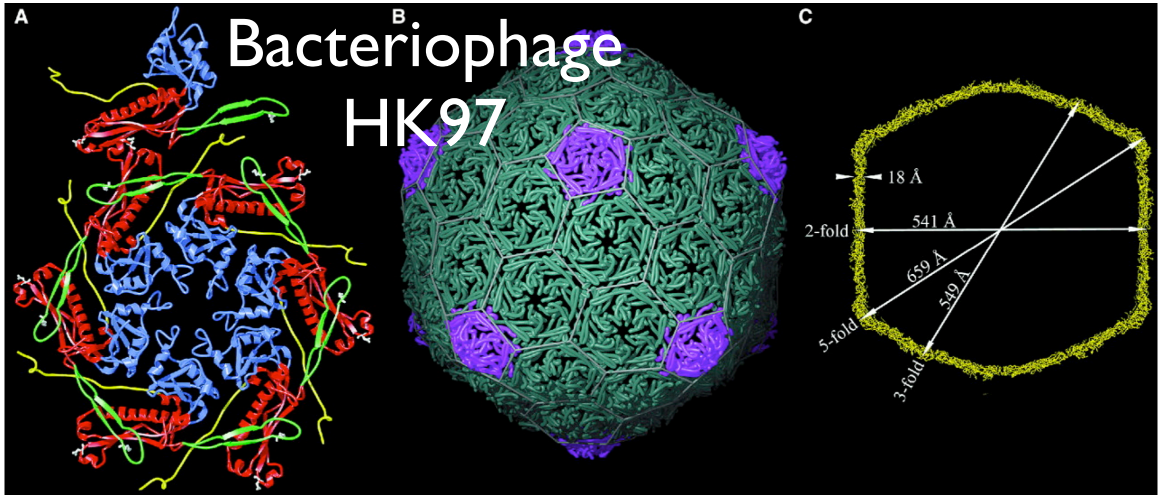
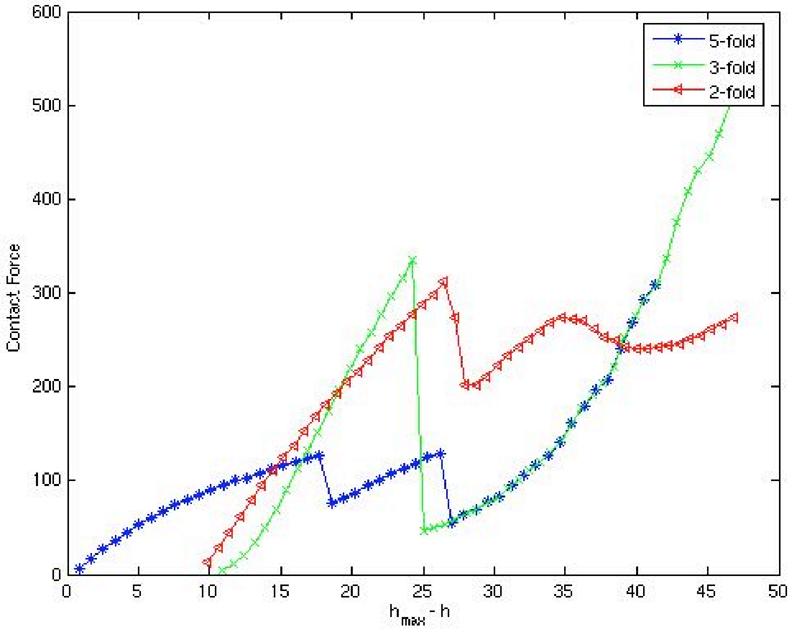
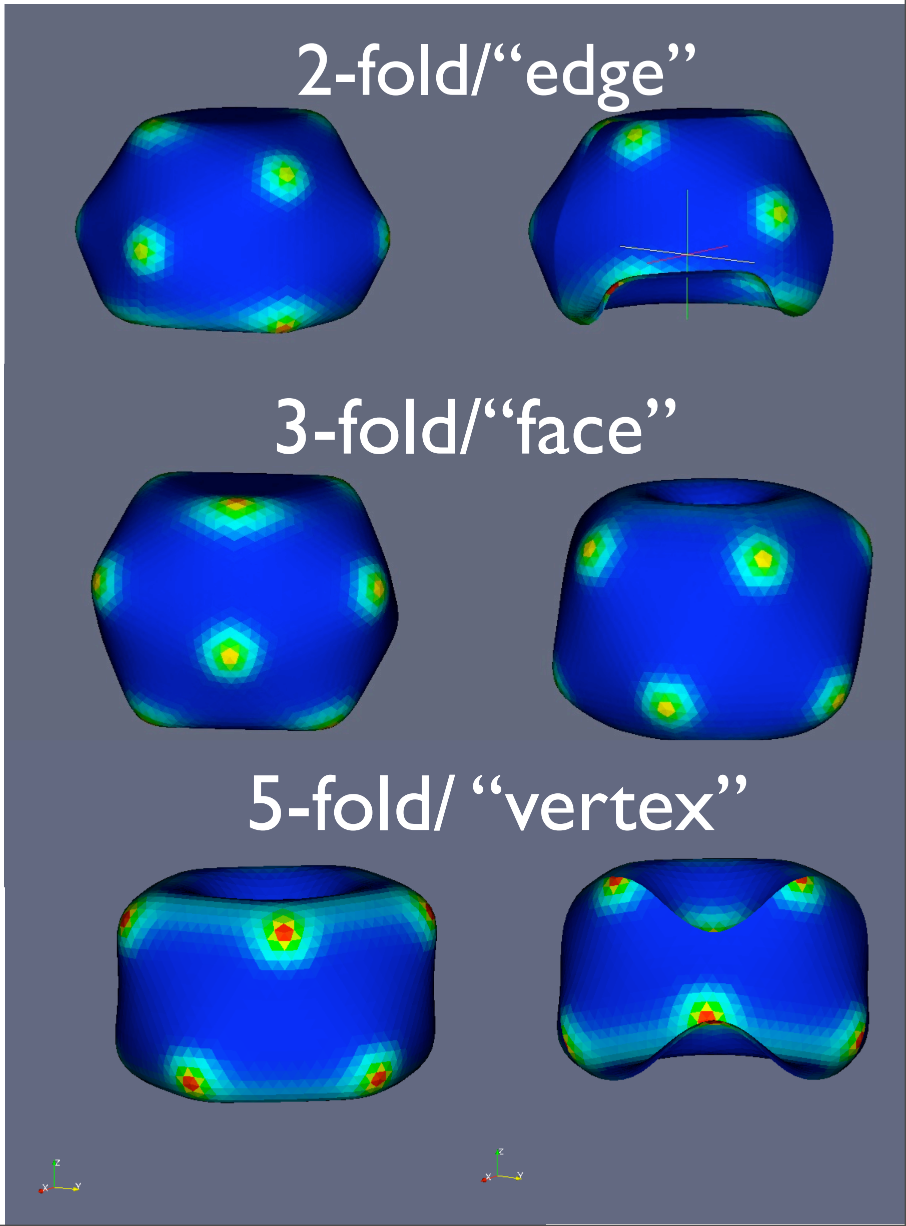
Orientation Dependence







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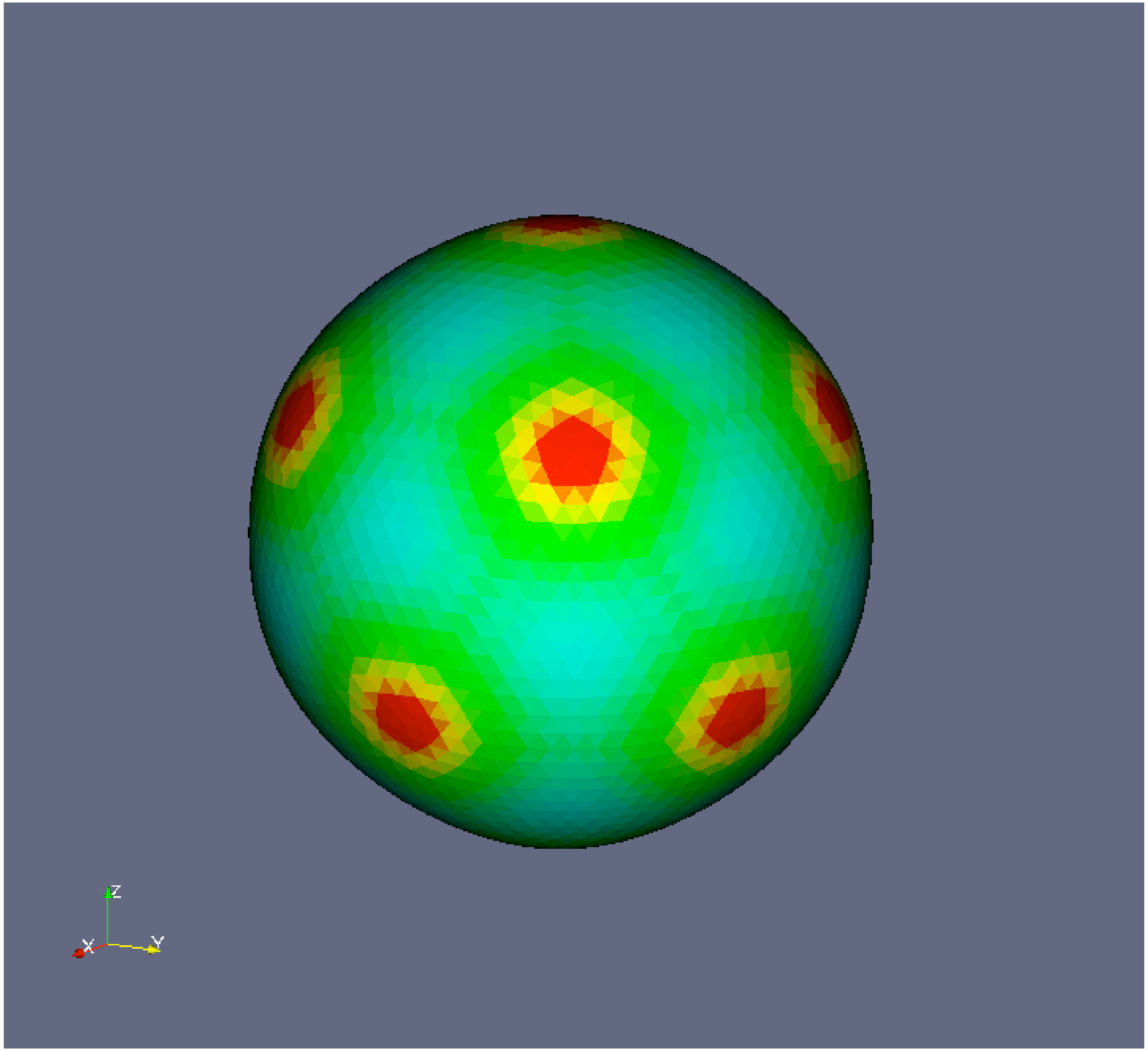
A small virus free to rotate



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Lessons from 2-D models

- 5-fold sites can act like structural imperfections, triggering instabilities
- Critical force/displacement varies with FvK
- Orientation stability varies with FvK

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Strategy for multi-scale modeling

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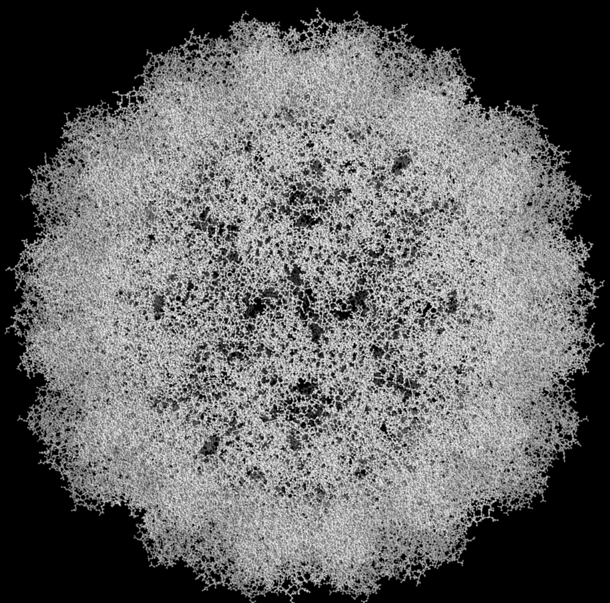
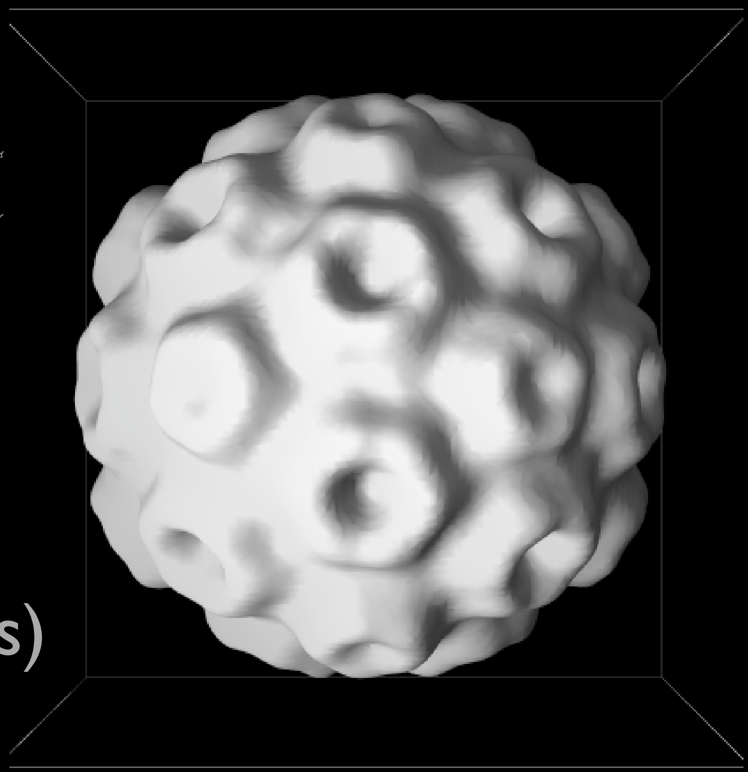
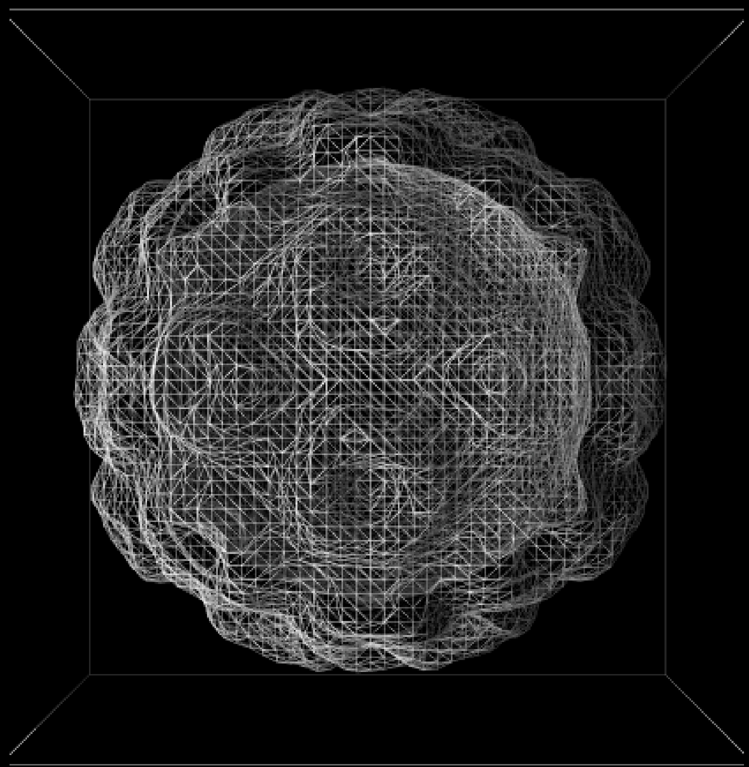
Strategy for multi-scale modeling



High resolution
(atomic coordinates)



Low resolution
(cryo-EM-like density)



Finite Element mesh

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