

How Does the Envelope (E) Protein of SARS-CoV-2 Induce Membrane Curvature?

Jesse Sandberg & Dr. Grace Brannigan

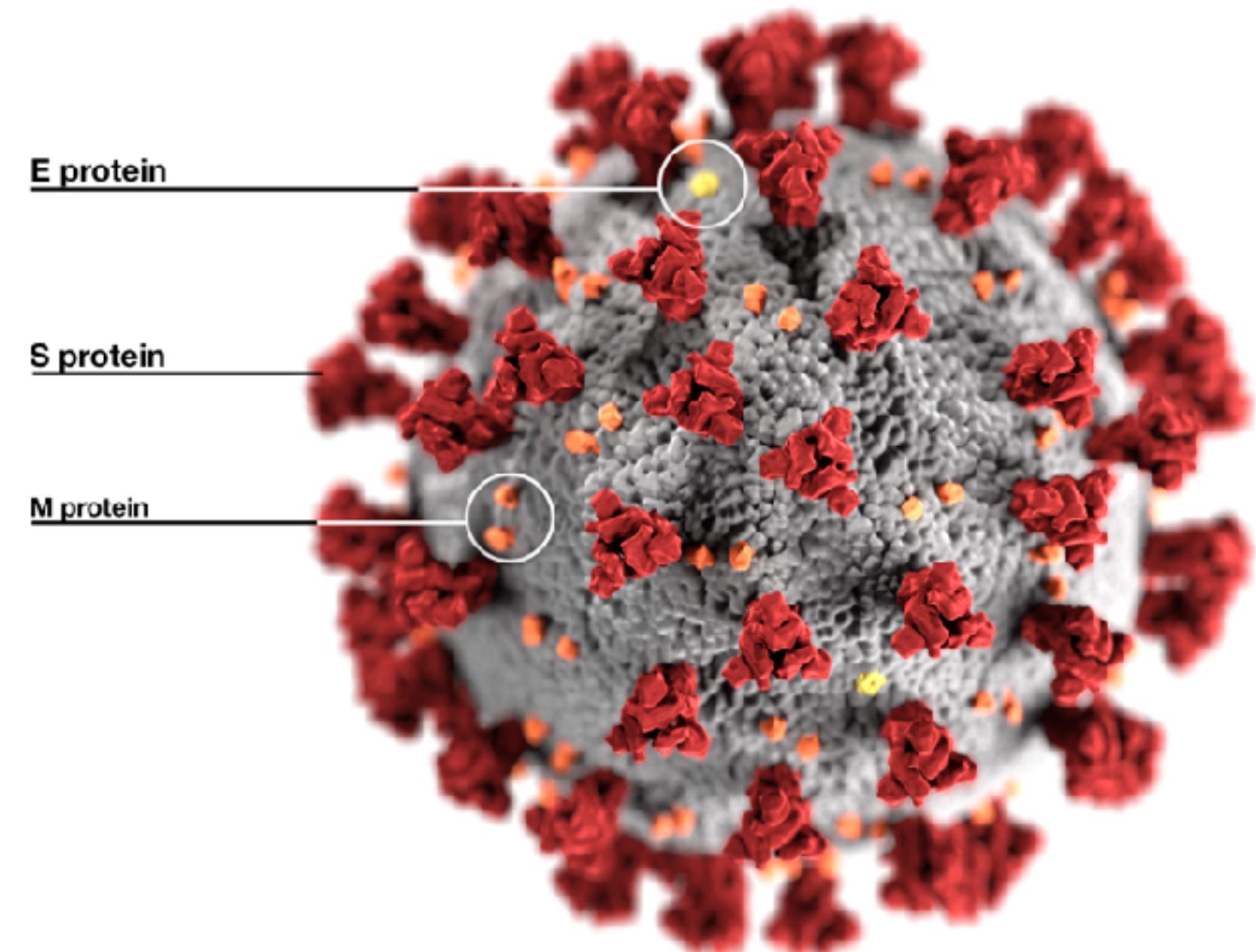
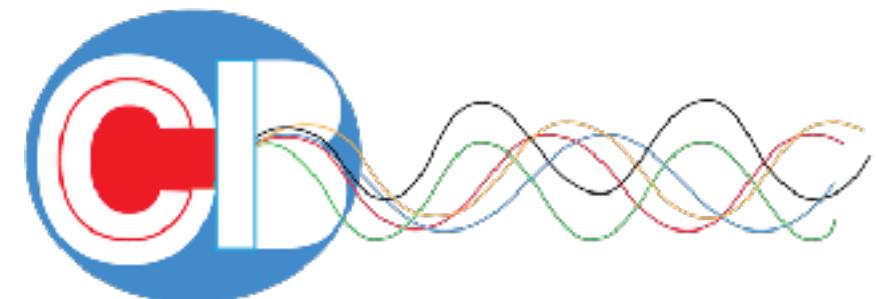
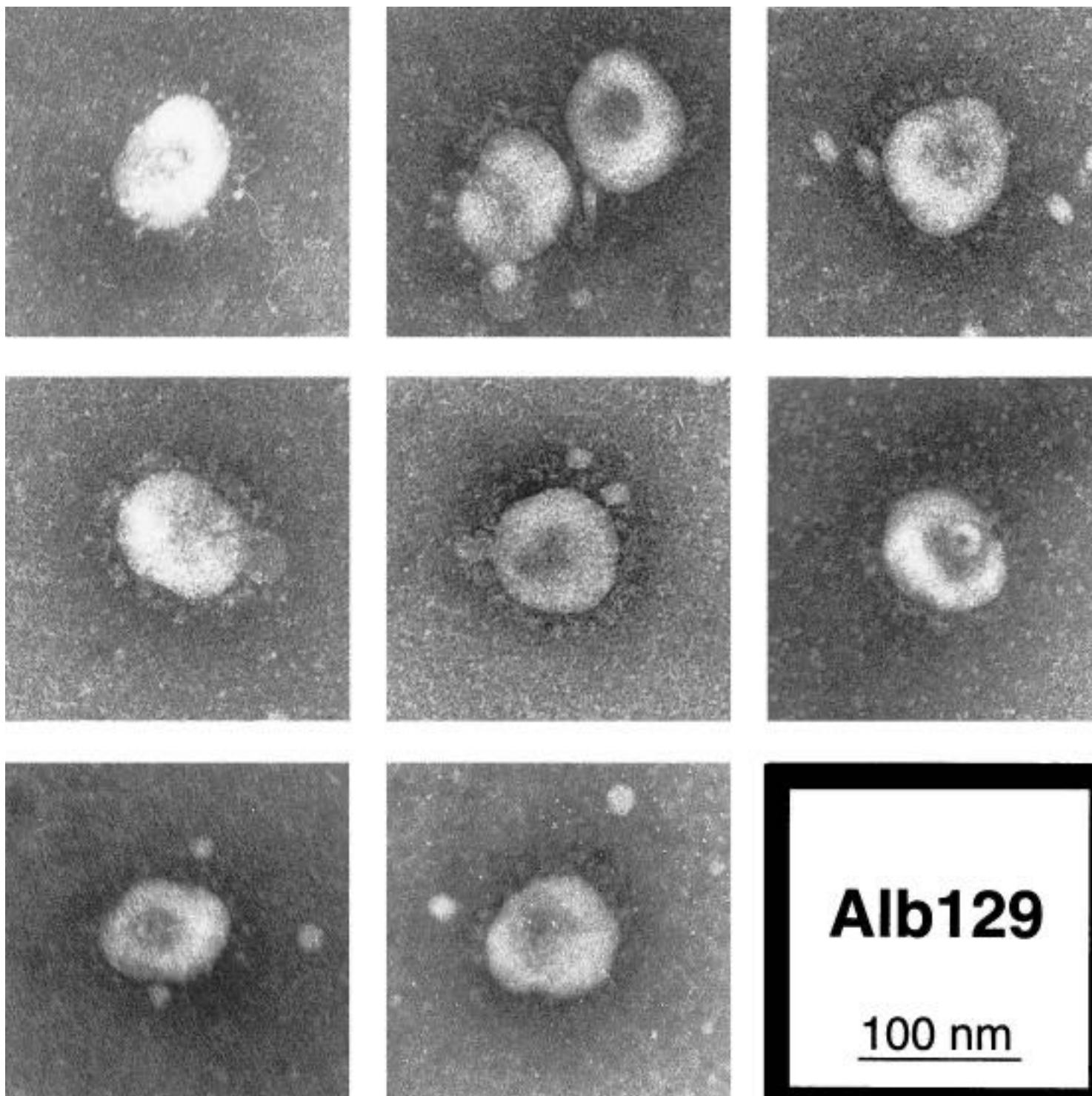
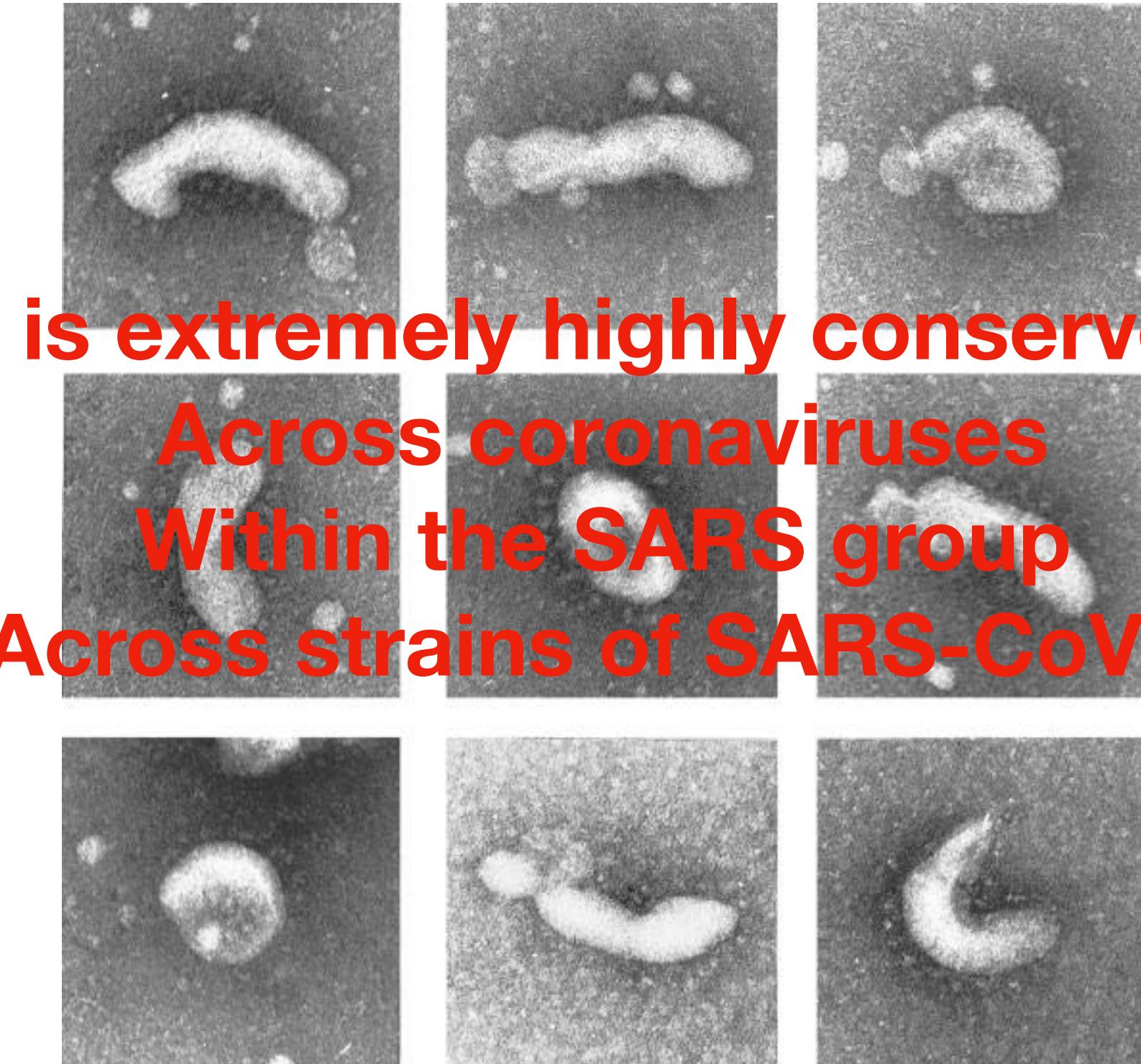


Photo Credit: CDC

E protein is crucial to virus



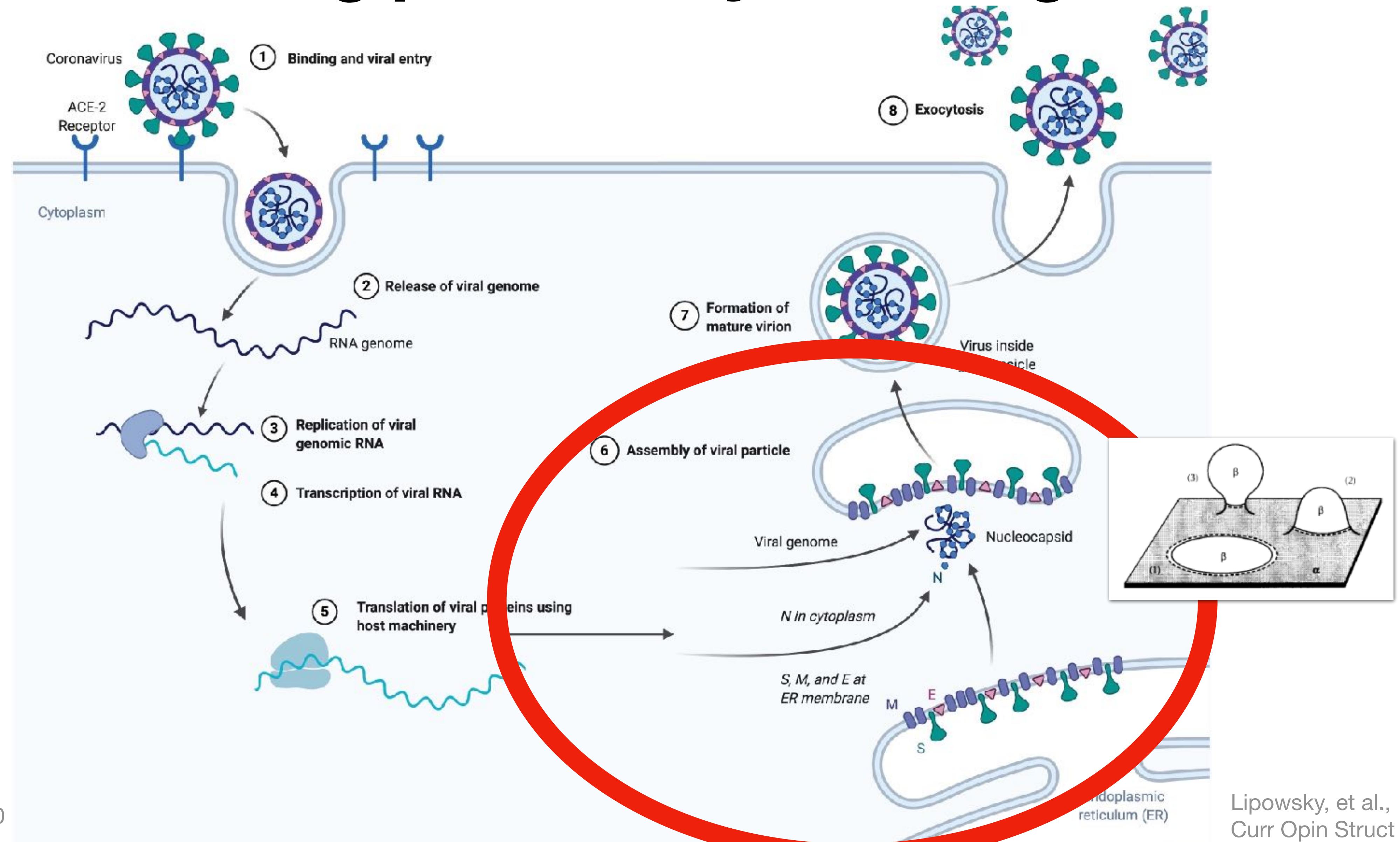
WT



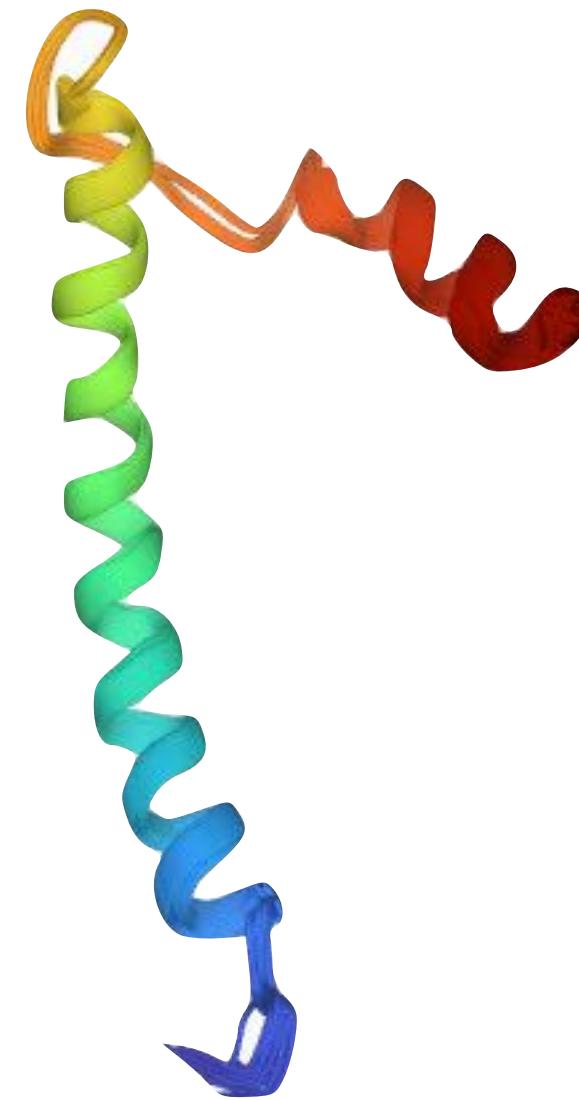
E mutant

E is extremely highly conserved:
Across coronaviruses
Within the SARS group
Across strains of SARS-CoV-2

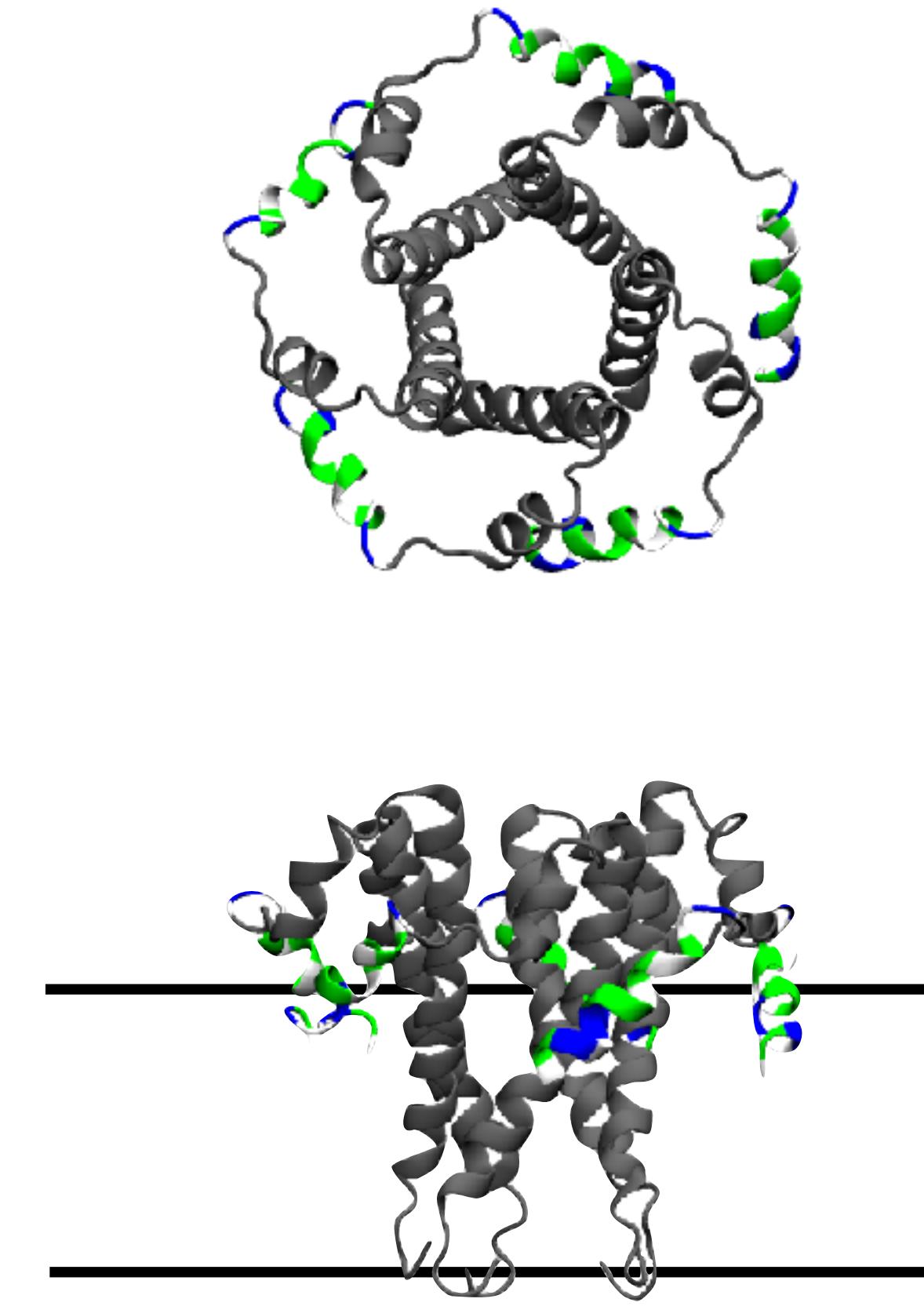
E drives budding process by inducing curvature



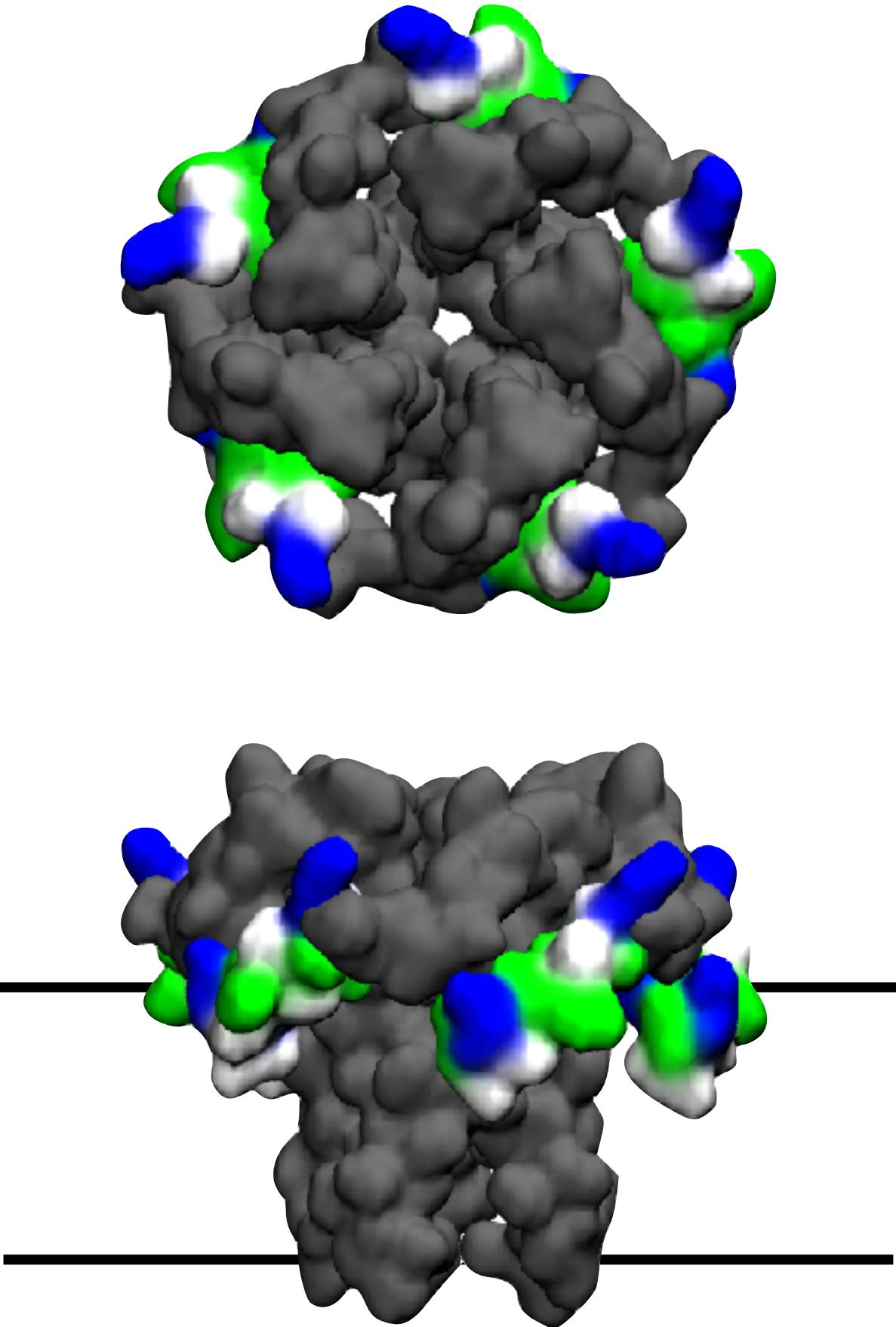
No known reason why such a small TM protein should bend a membrane



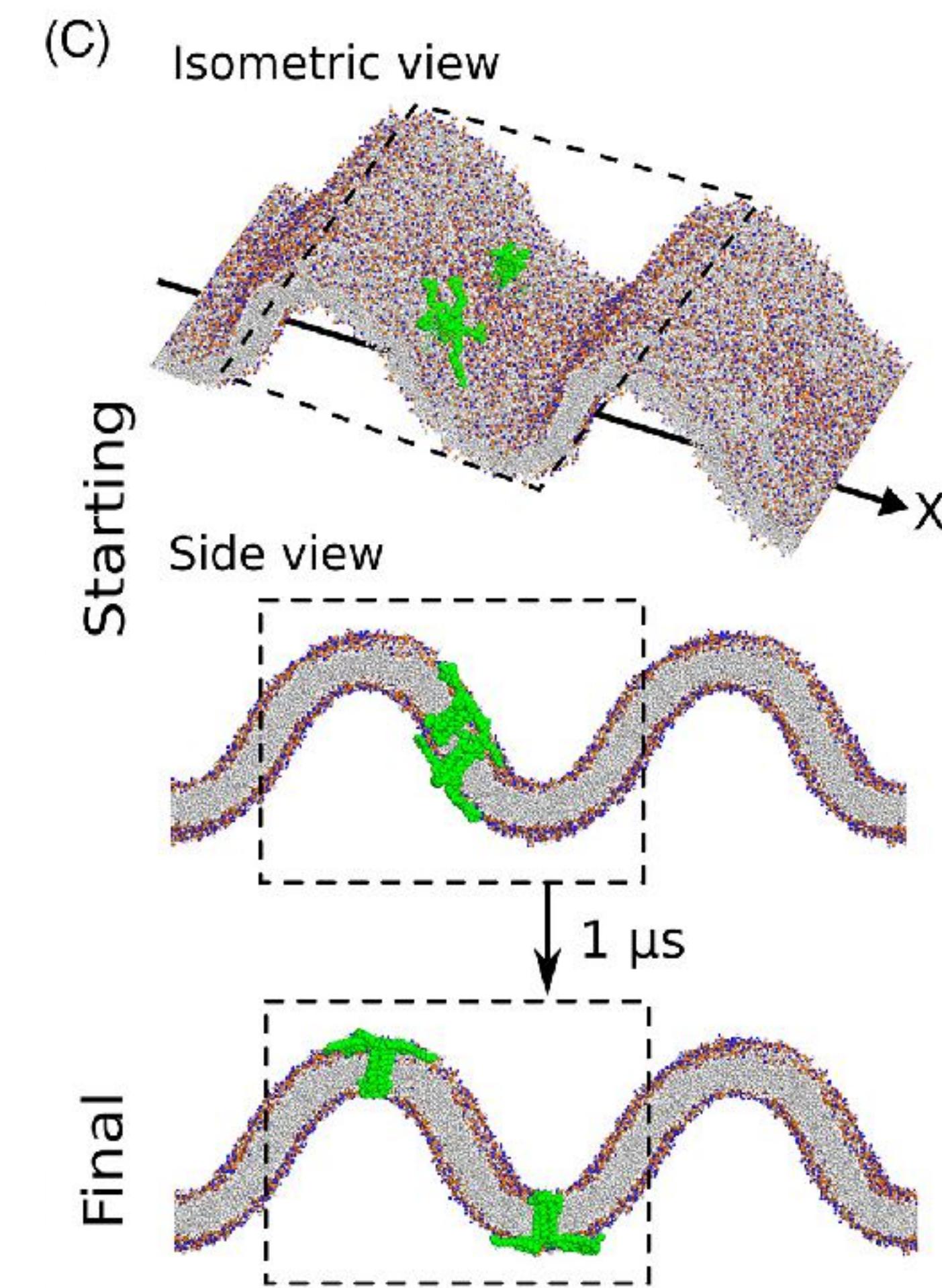
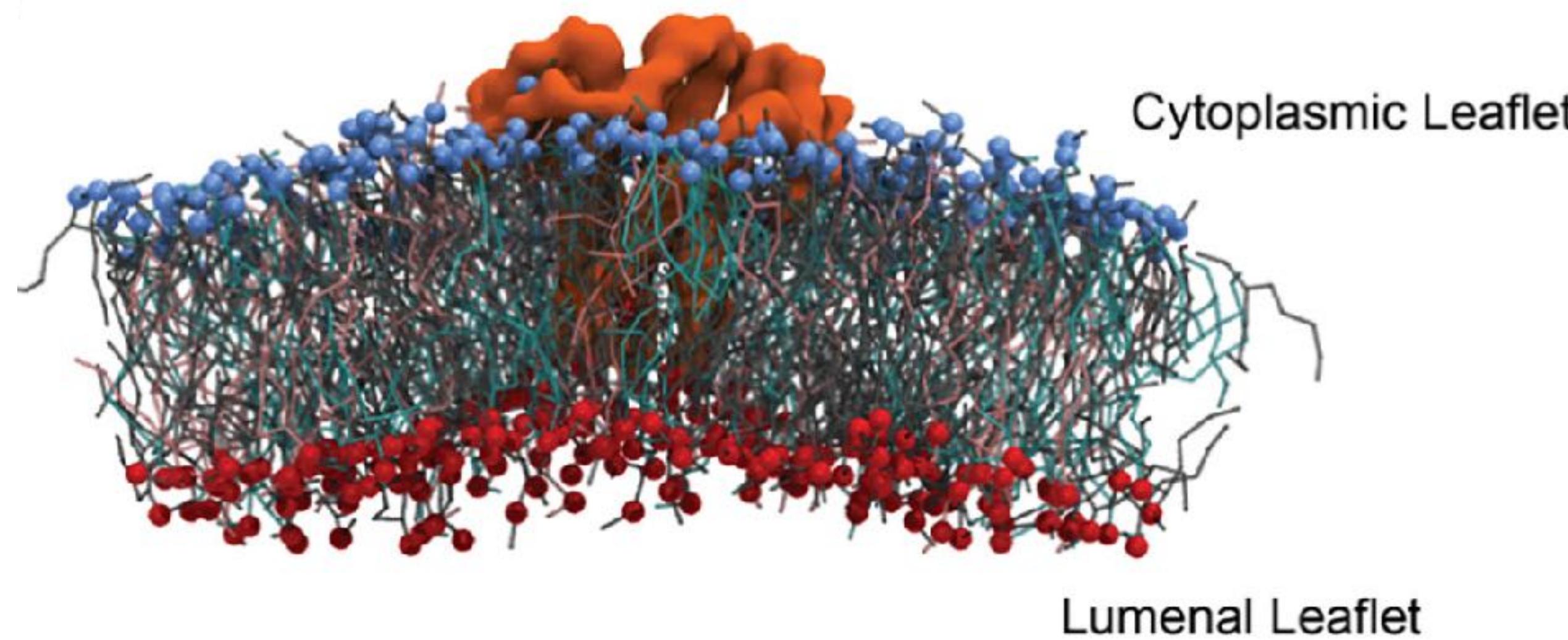
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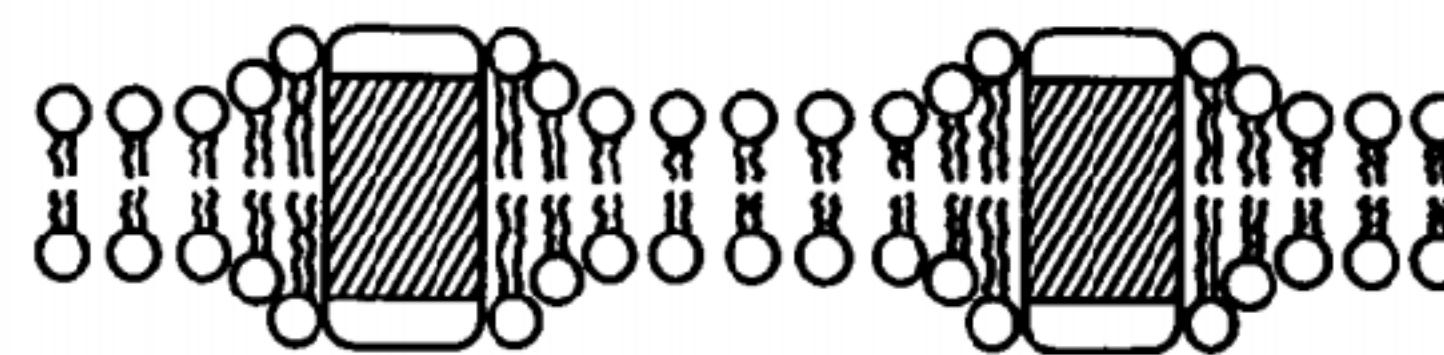
PDB ID: 5X29



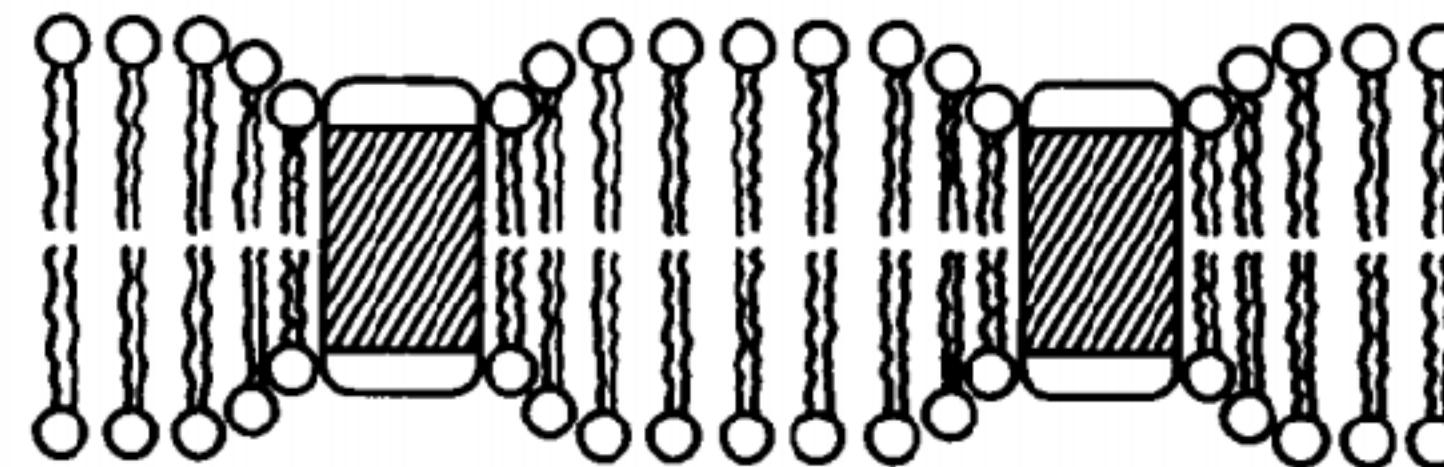
Computational Groups Confirm E's Bending Role



Research focus: How does E induce curvature?

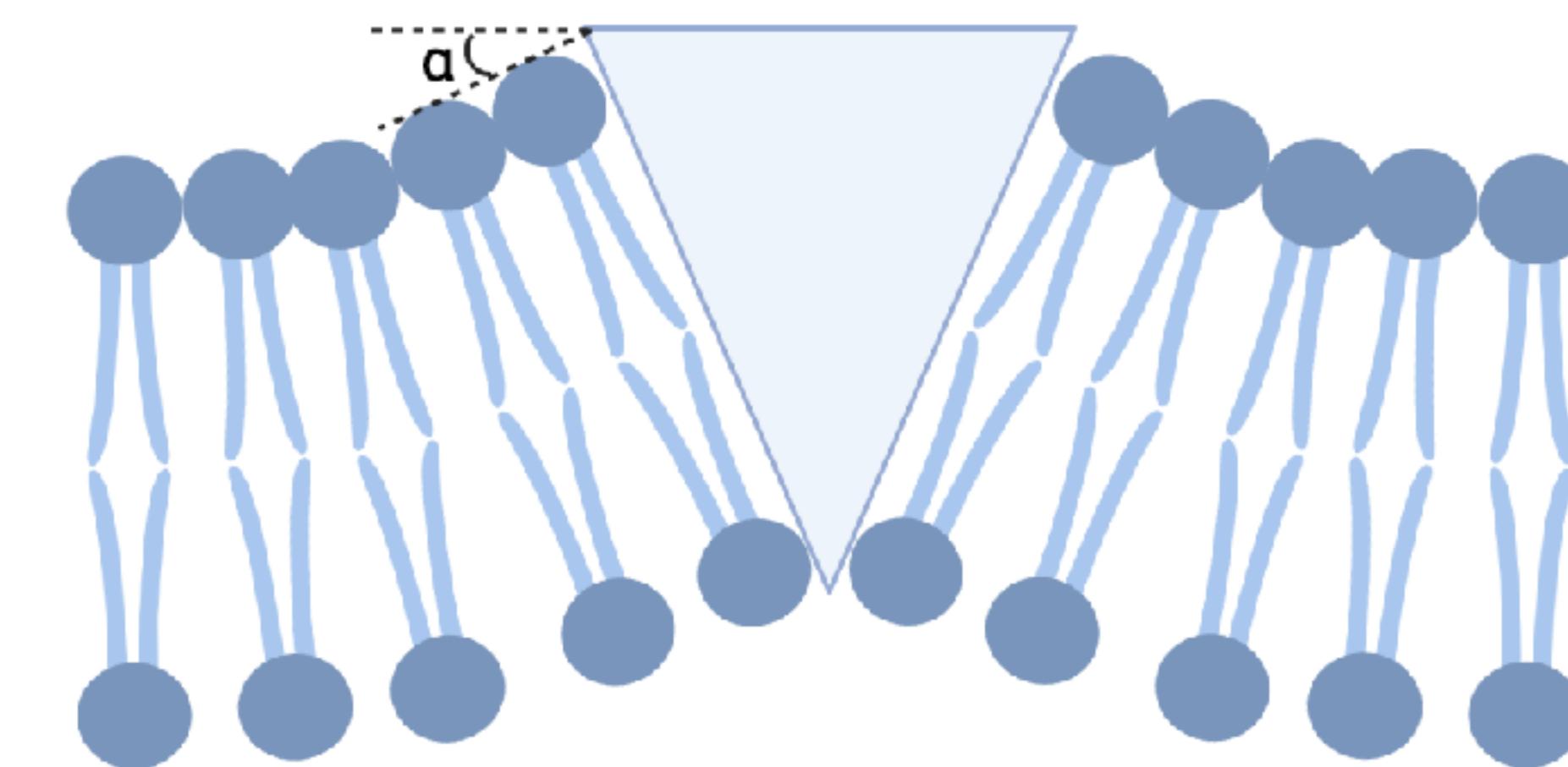


a



b

Hydrophobic Mismatch Mechanism



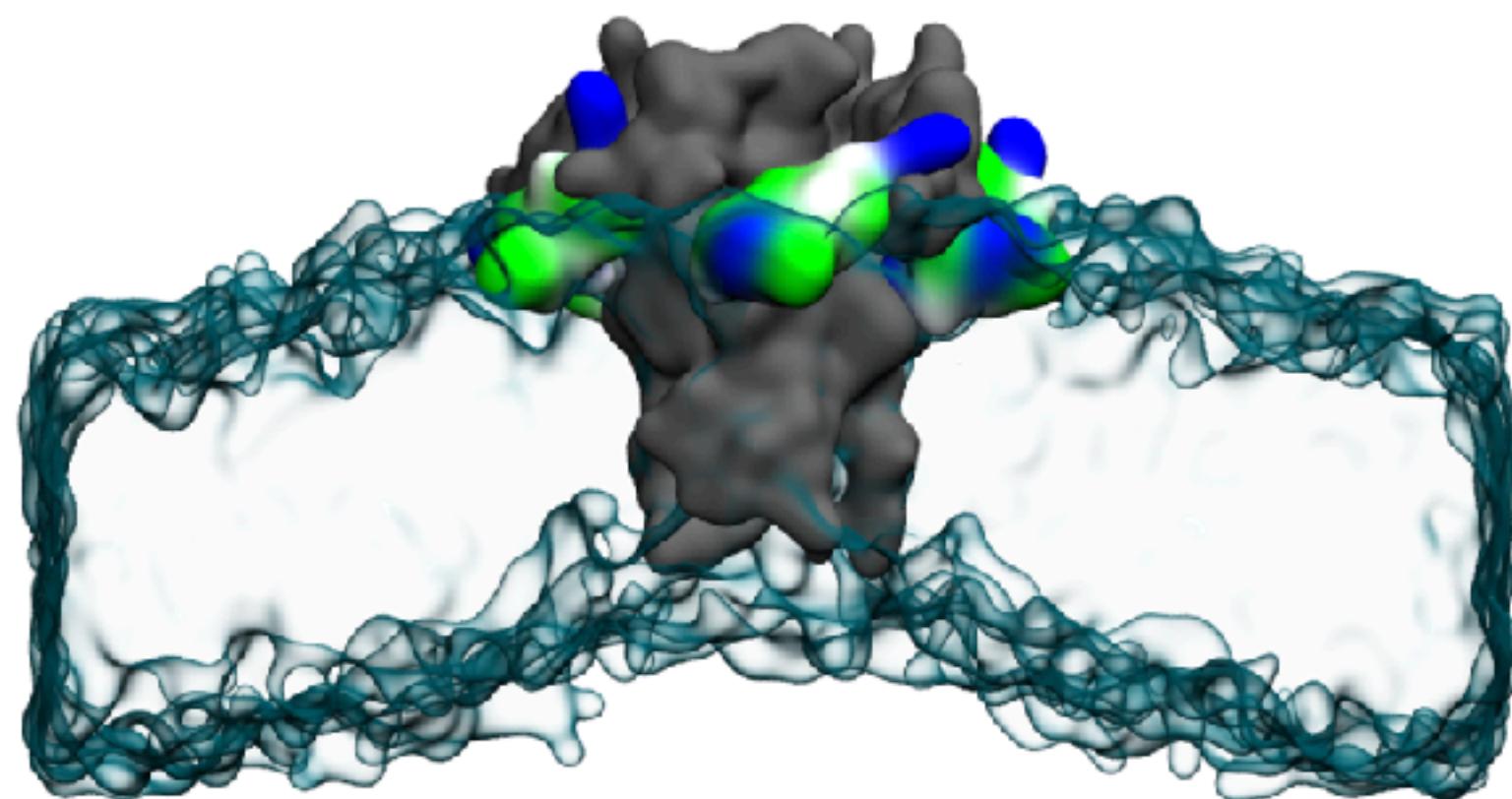
Contact Angle Mechanism

Research Questions

- 1. What happens at a more physiological concentration?**
- 2. Is it a hydrophobic mismatch mechanism?**
- 3. Is it a contact angle mechanism?**

Research Questions

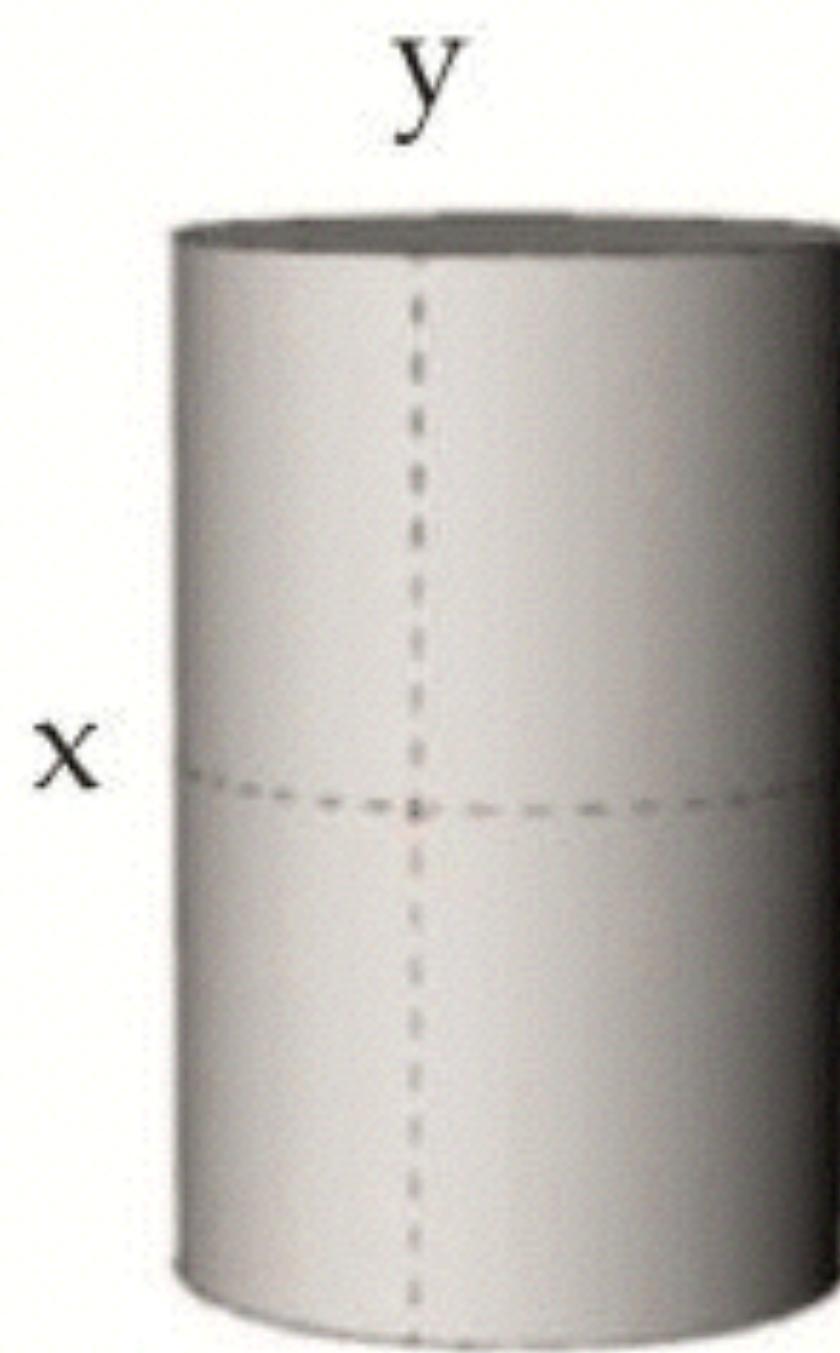
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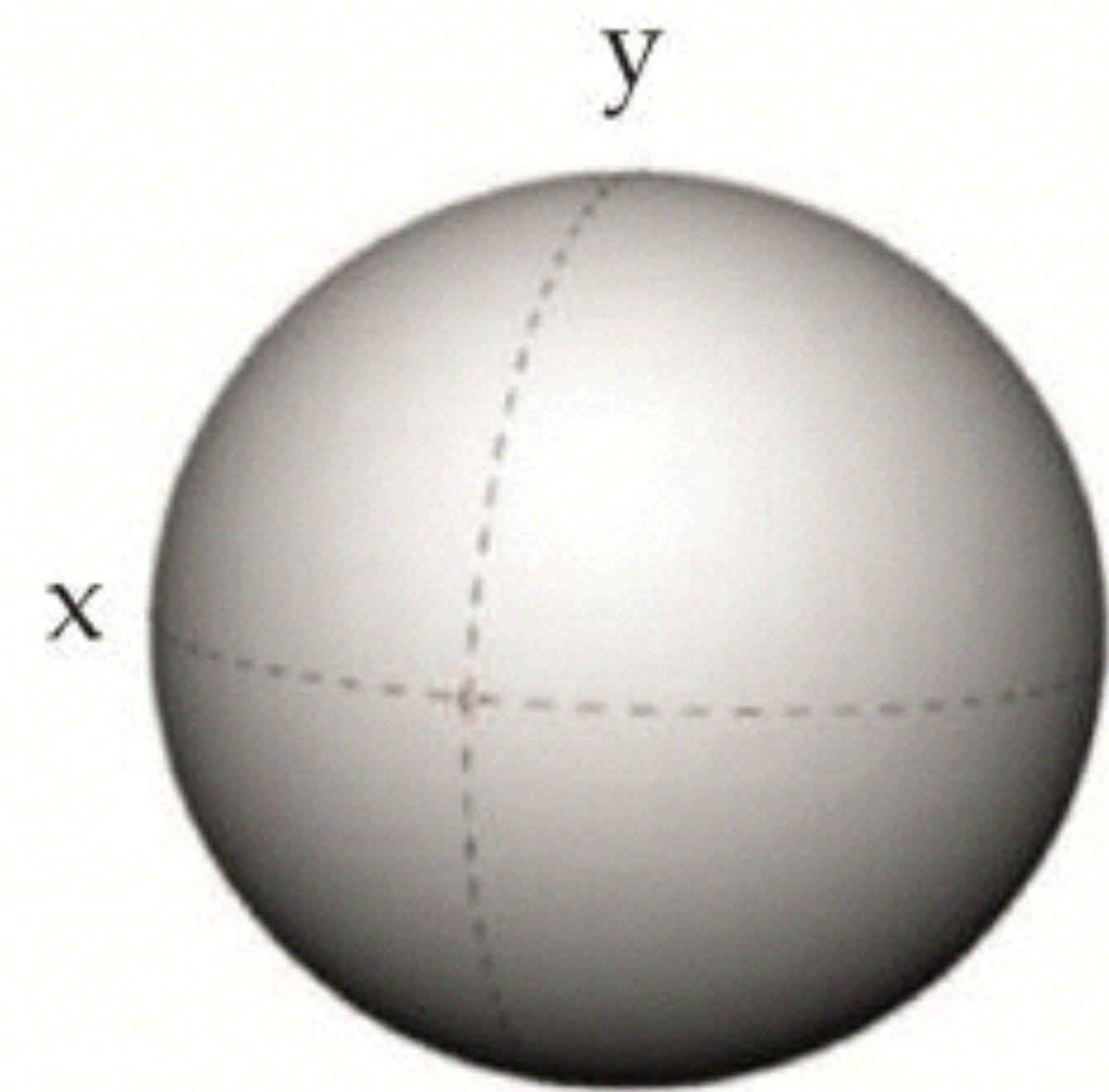
Quick math refresher!



Saddle Point

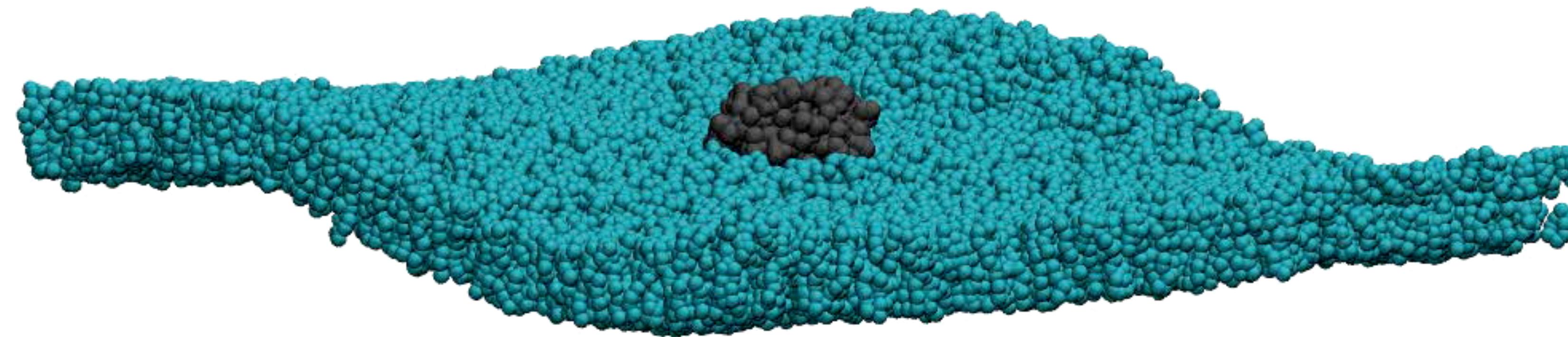


Cylinder



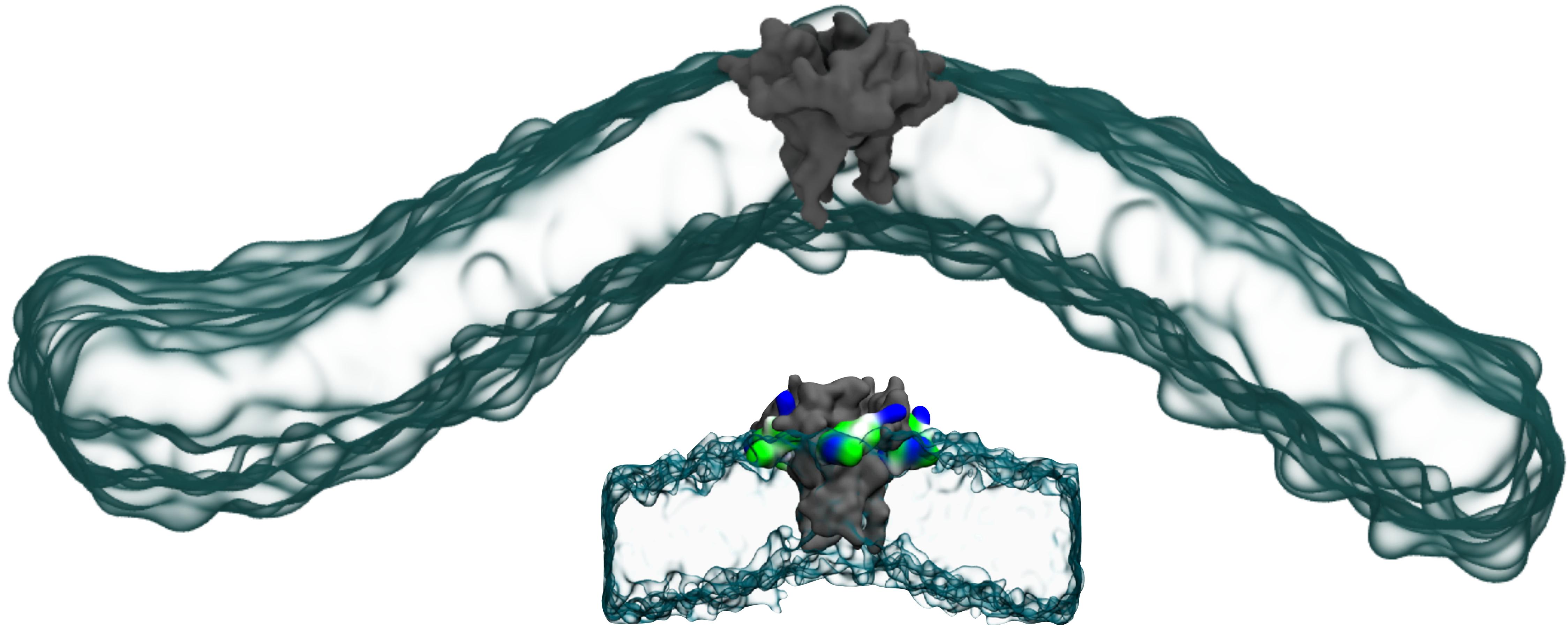
Sphere

Bending Increases With Box Size



**Simulation box is 40x40 nm
POPC and protein shown; water and ions hidden**

Signal does not attenuate as expected



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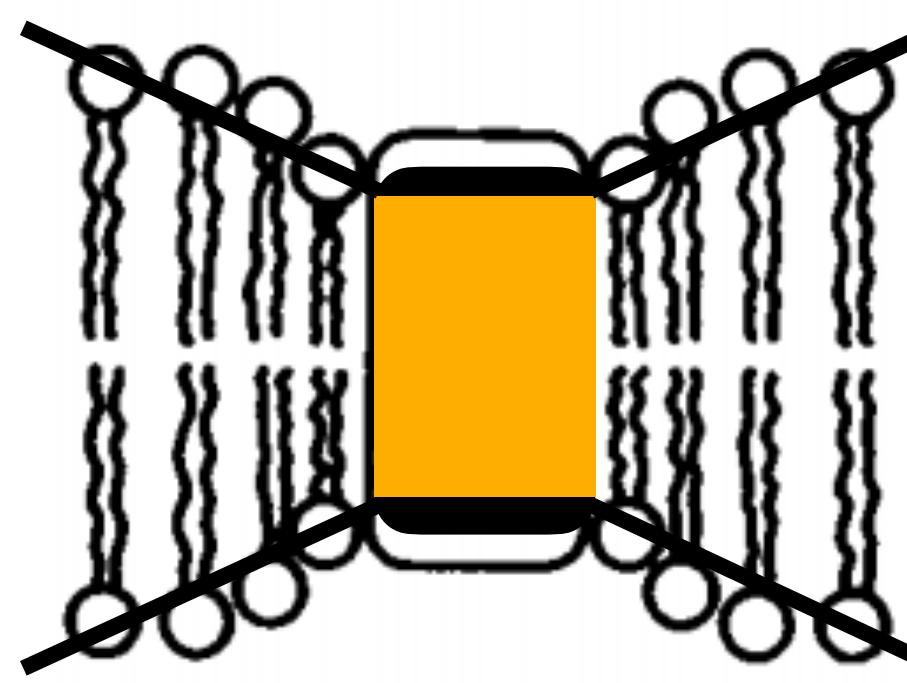
Bending increases substantially in POPC system!

Need to rerun all systems in larger boxes!

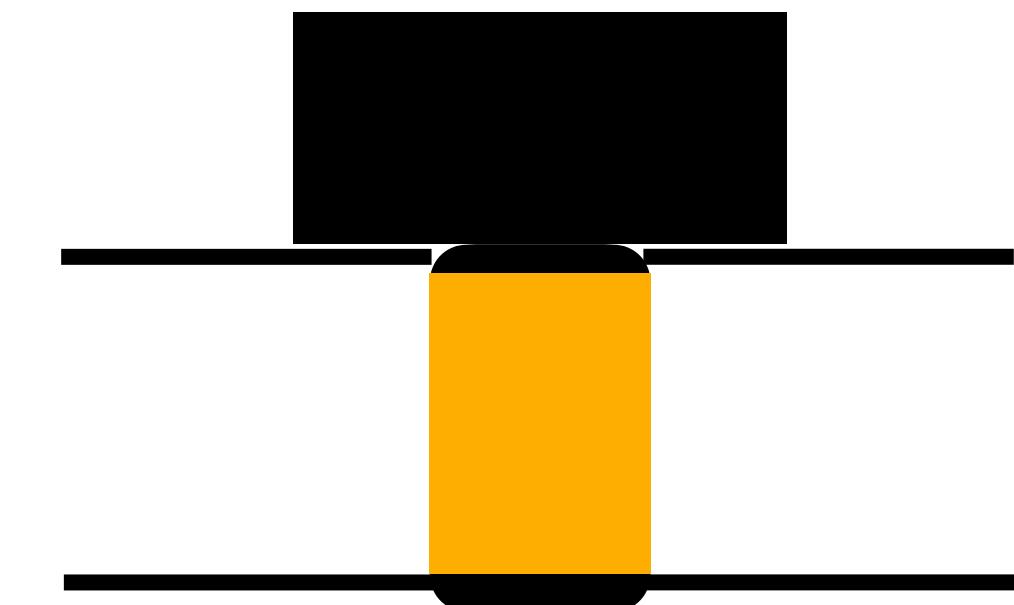
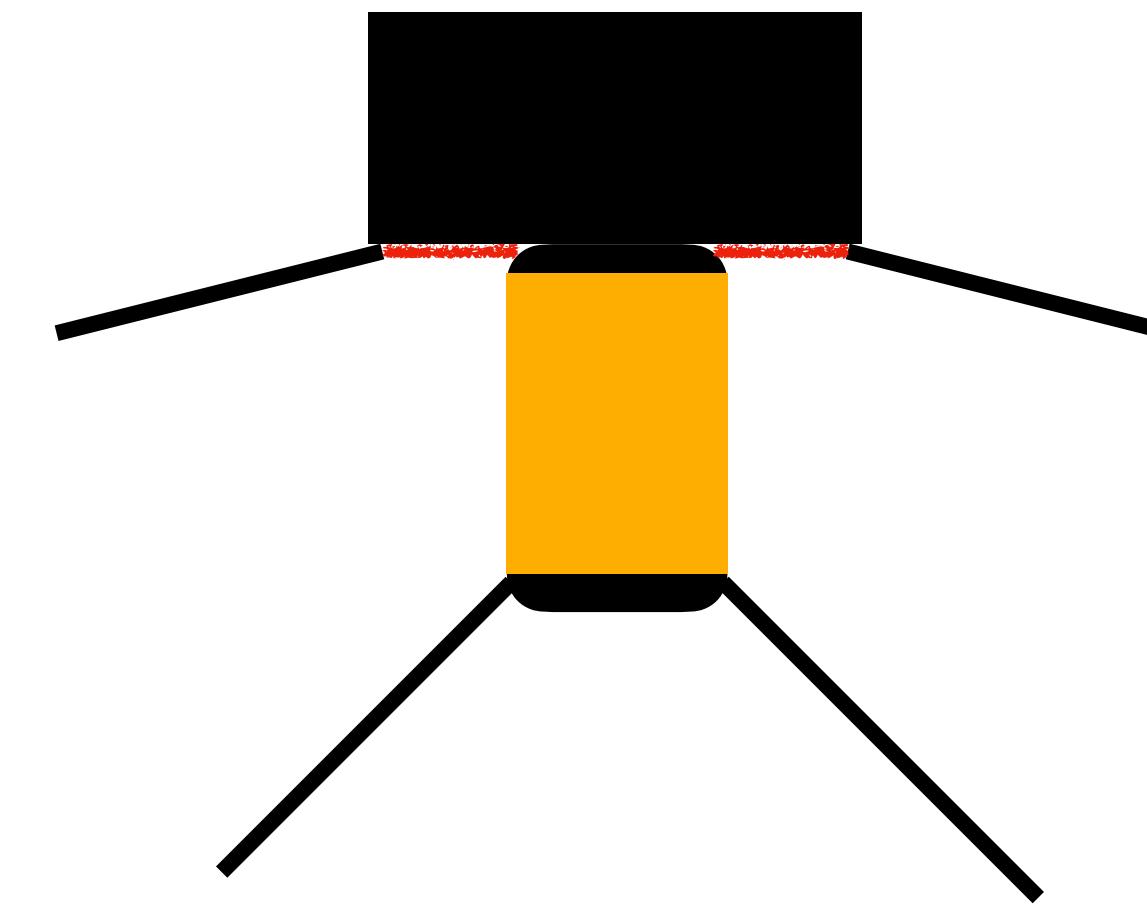
Research Questions

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How could this be hydrophobic mismatch?

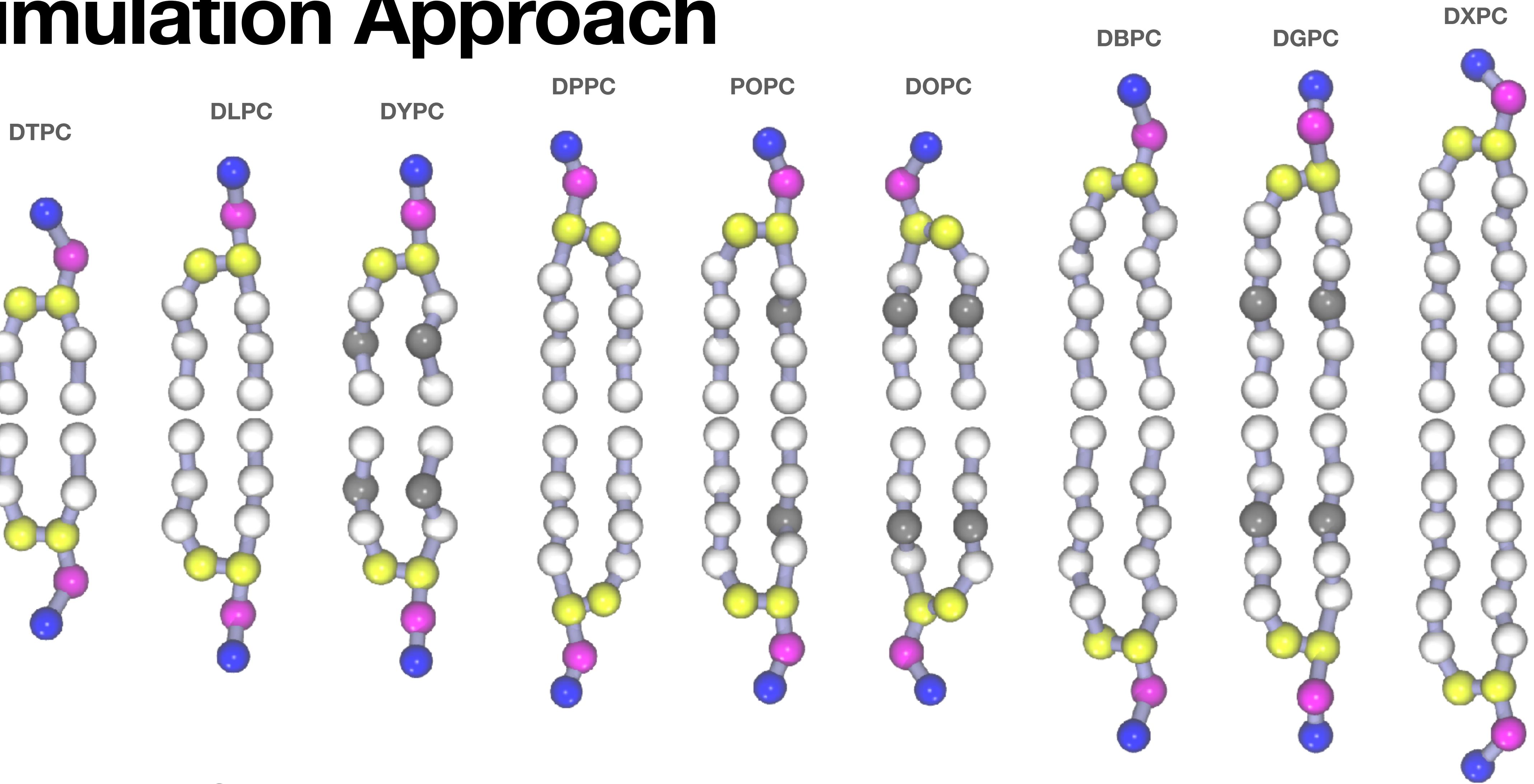


Hydrophilic
Hydrophobic



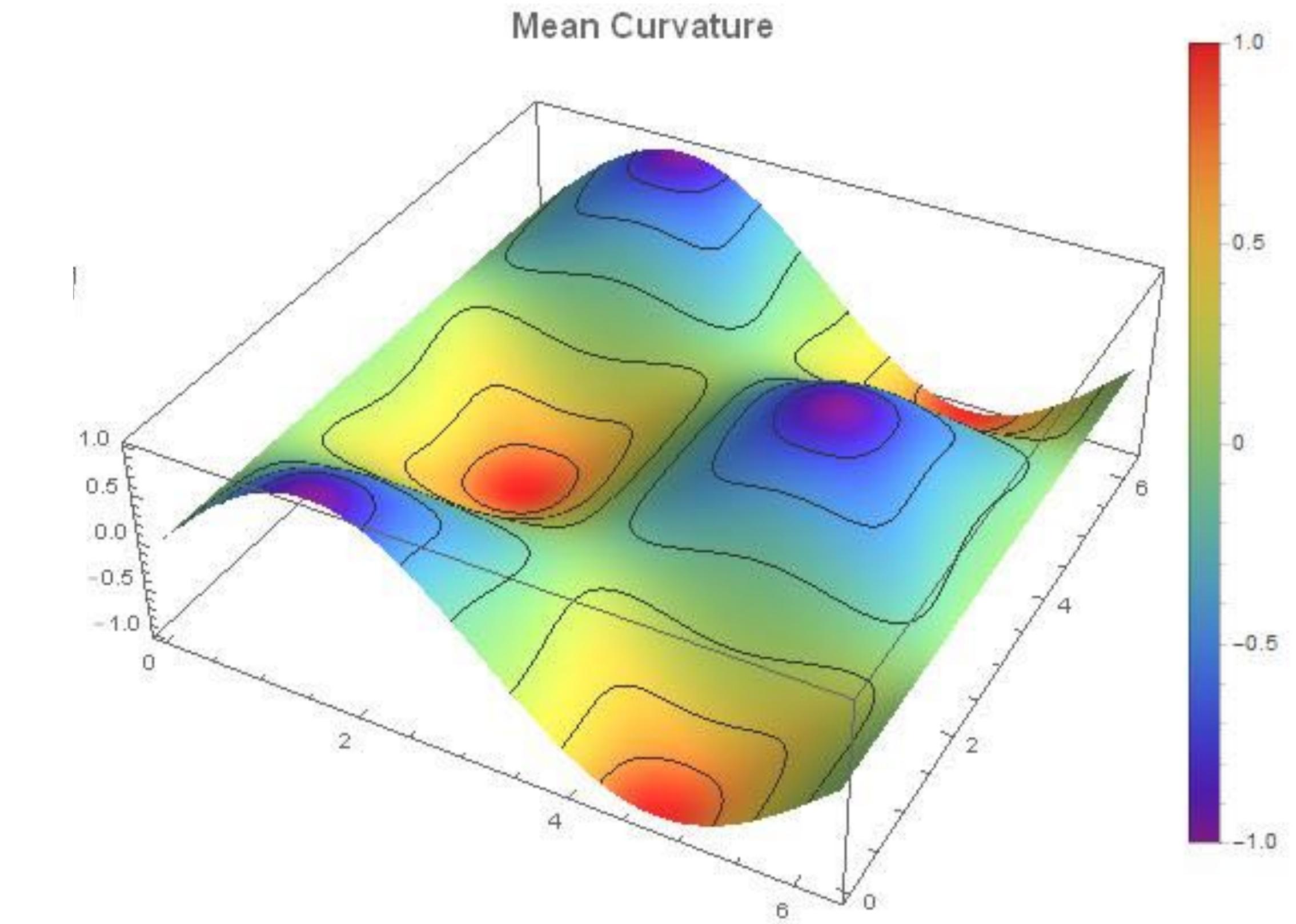
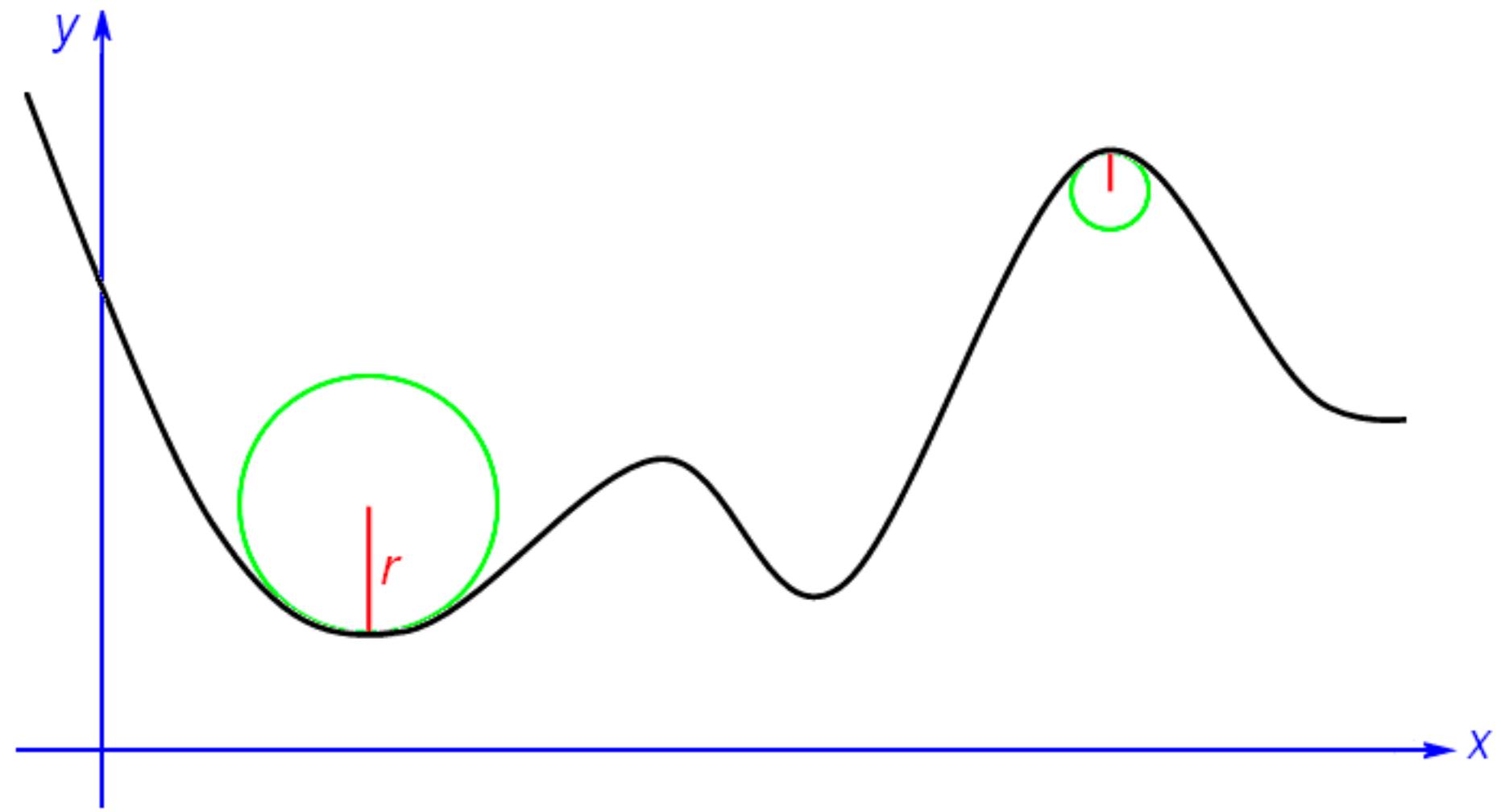
How would this change
If we shortened the lipids?

Simulation Approach



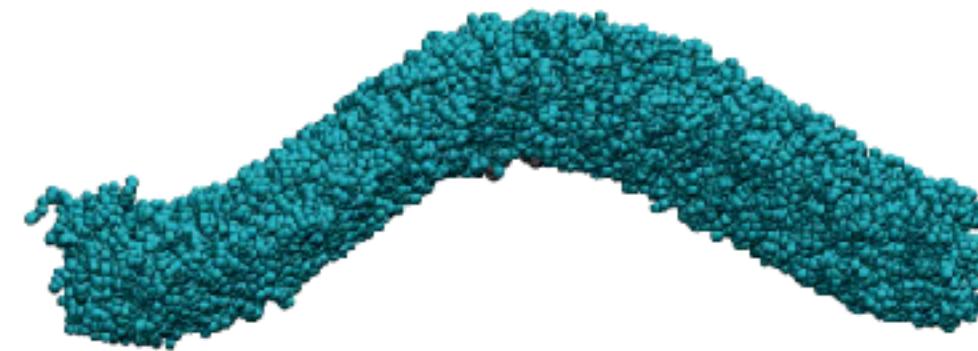
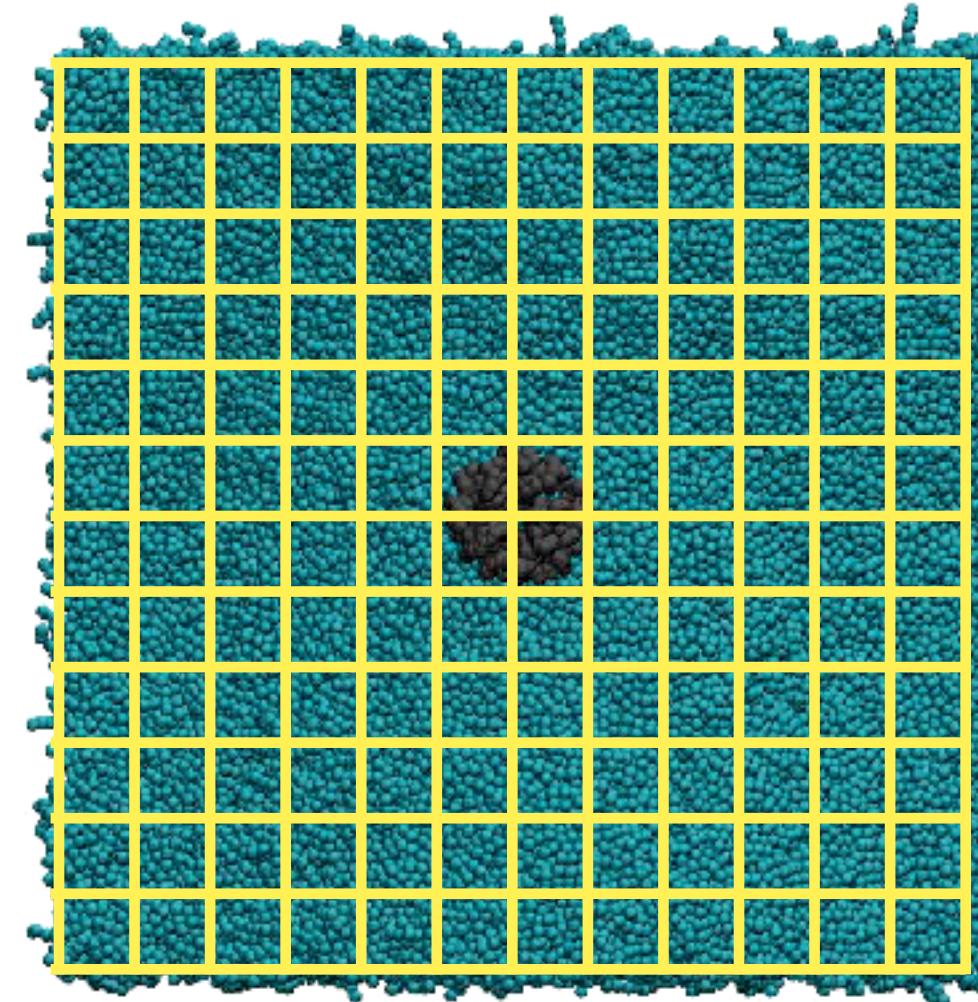
**Simulate with different lipid length and saturation level
to observe differences in membrane deformation**

To quantify differences between systems, measure curvature

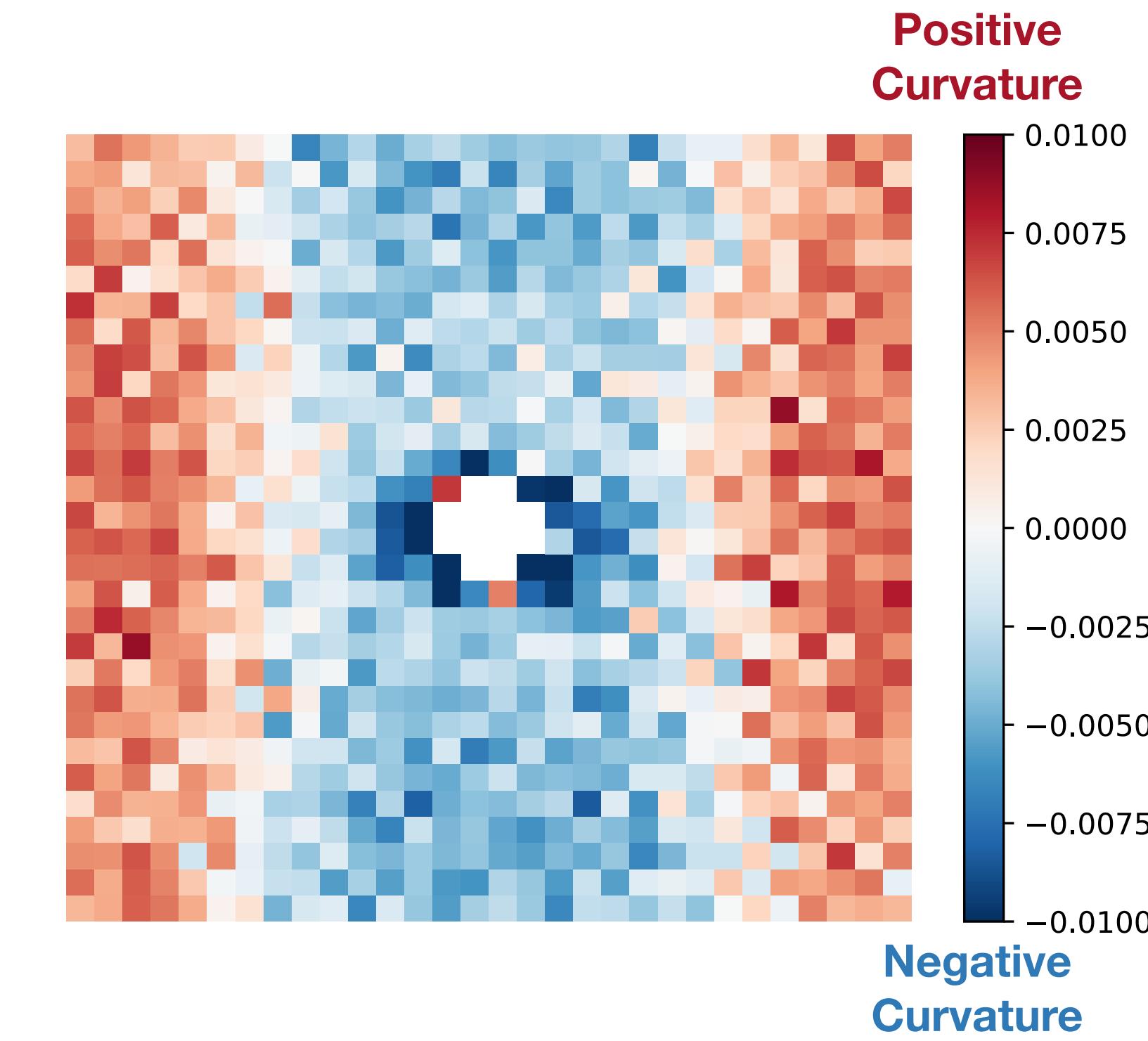
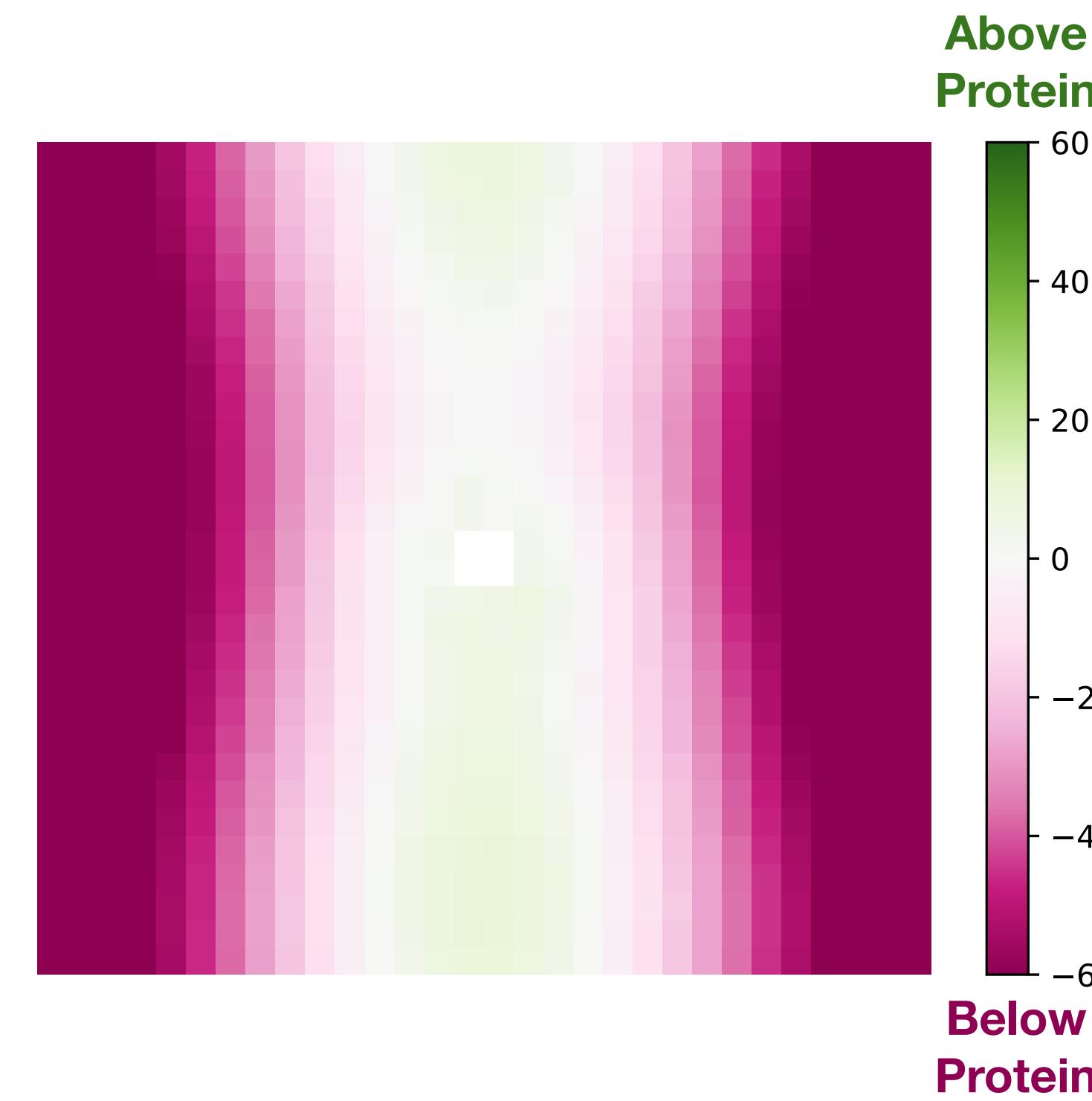


In my systems, mean curvature reduces to the laplacian: $\frac{\partial^2 z}{\partial x^2} + \frac{\partial^2 z}{\partial y^2}$

nougat: a tool for simulation analysis



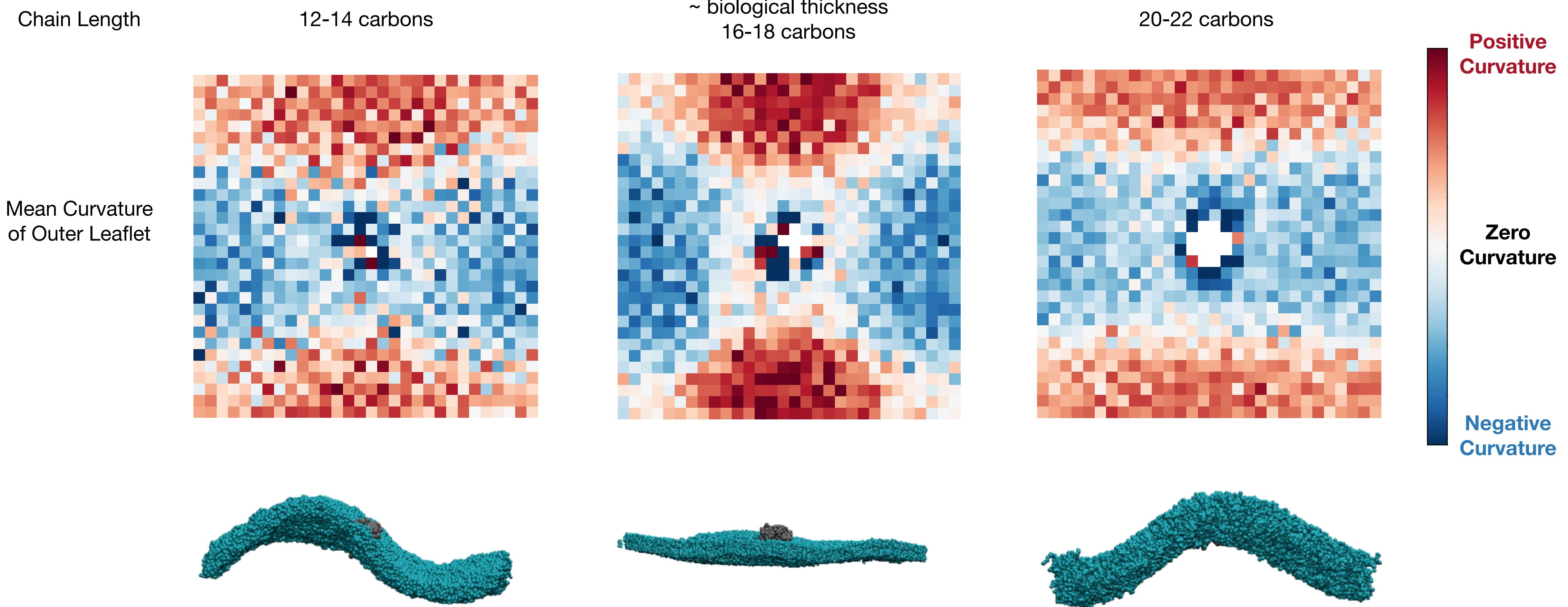
MD Simulation



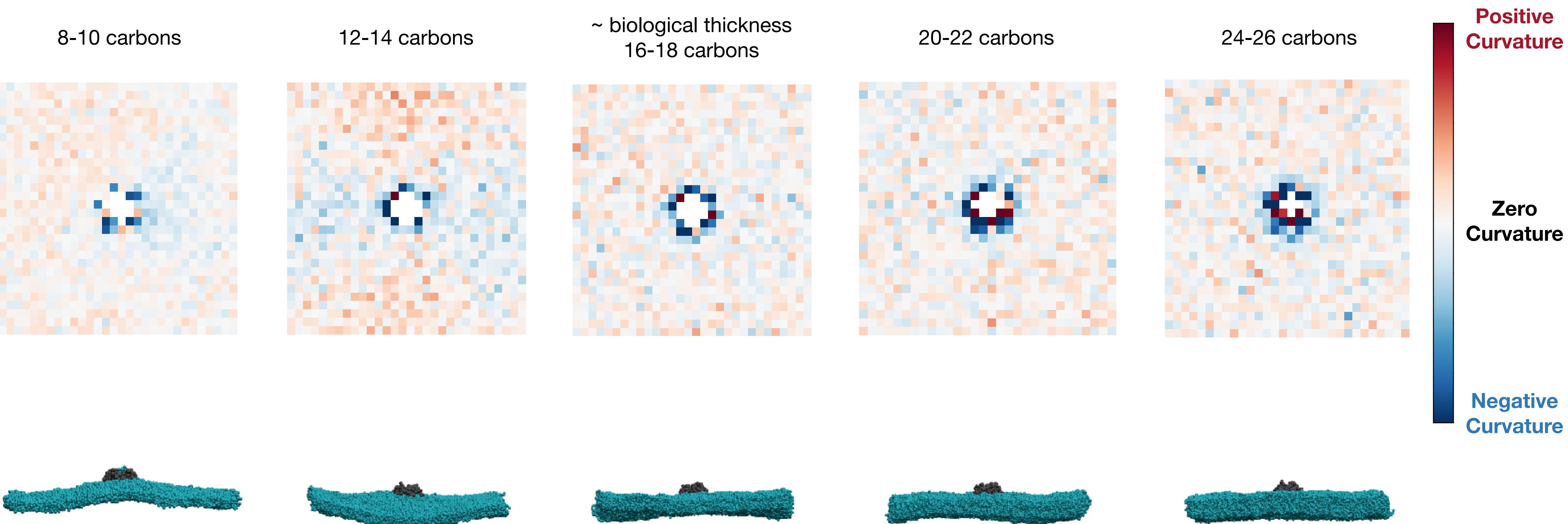
nougat Curvature Plot

[BranniganLab / nougat](#) Public

Unsaturated lipids show strong bending, no trend



Saturated lipids show no bending, only local deformation



Research Questions

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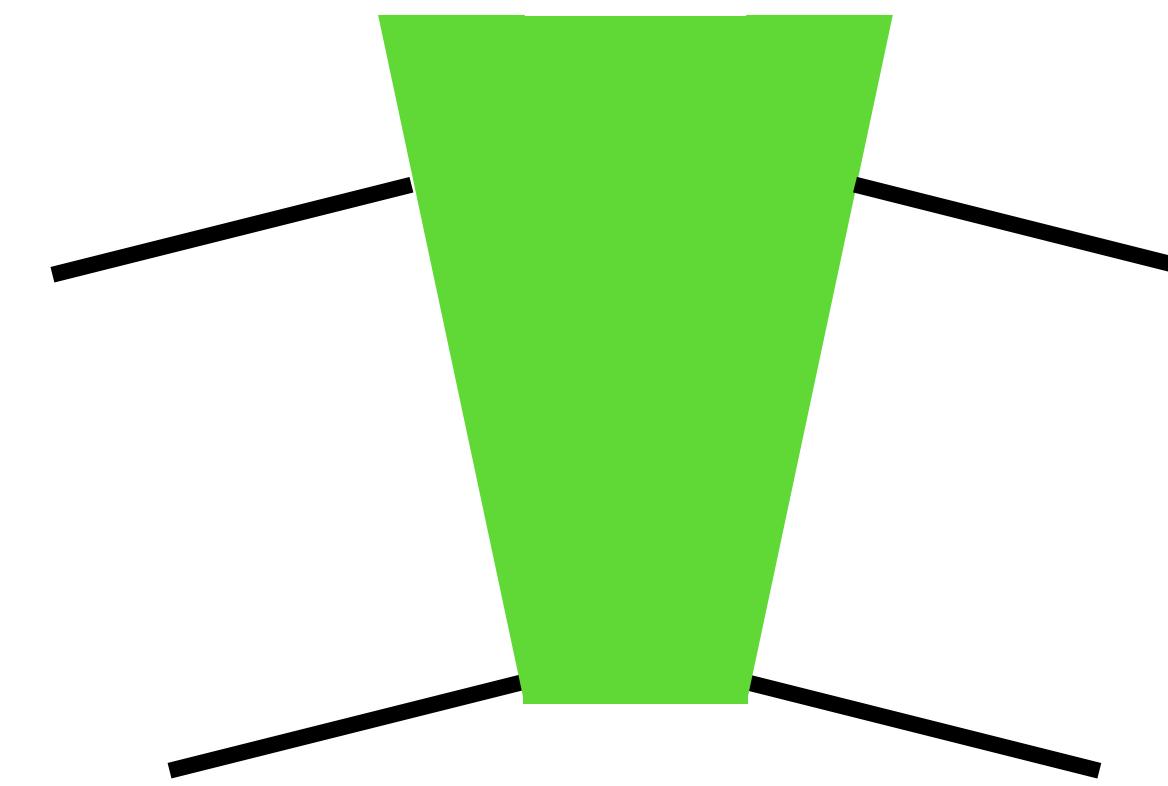
Hydrophobic mismatch may explain local deformations

Does not explain large-scale bending

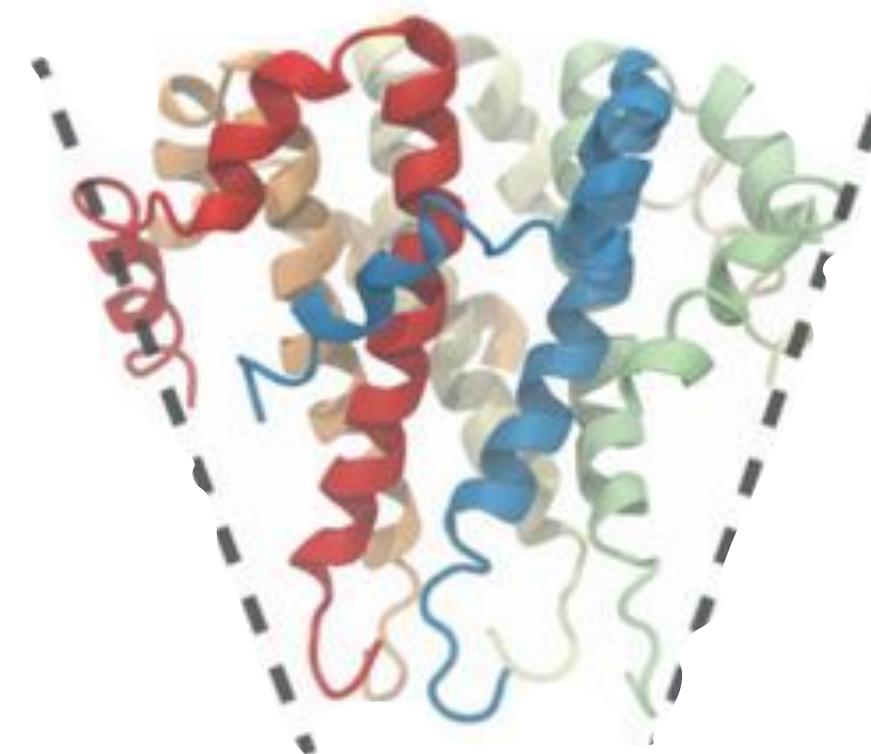
Research Questions

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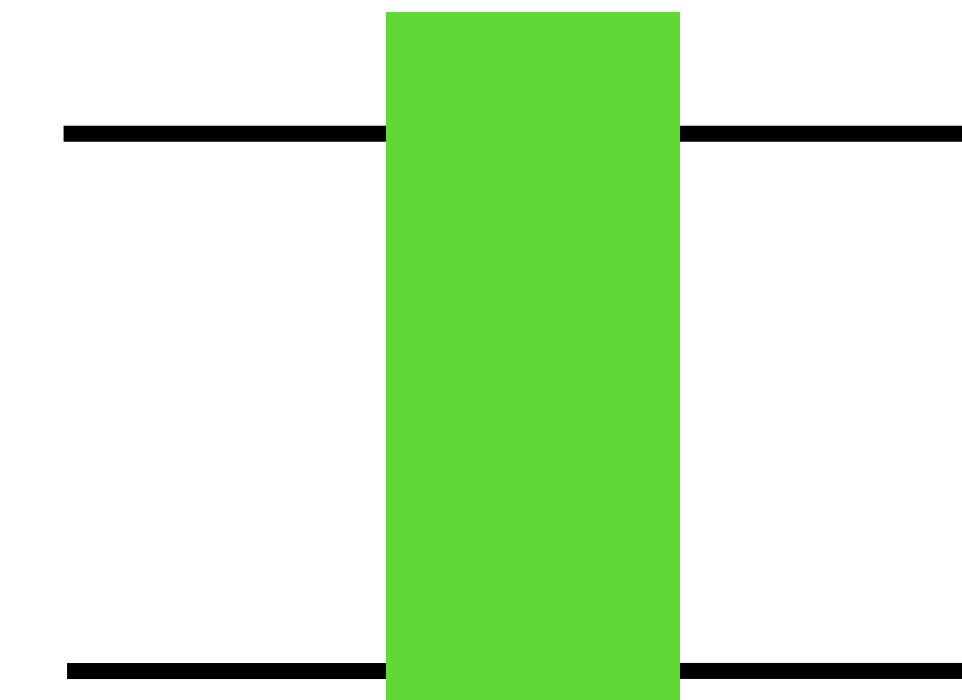
Does bending stop if we remove contact angle?



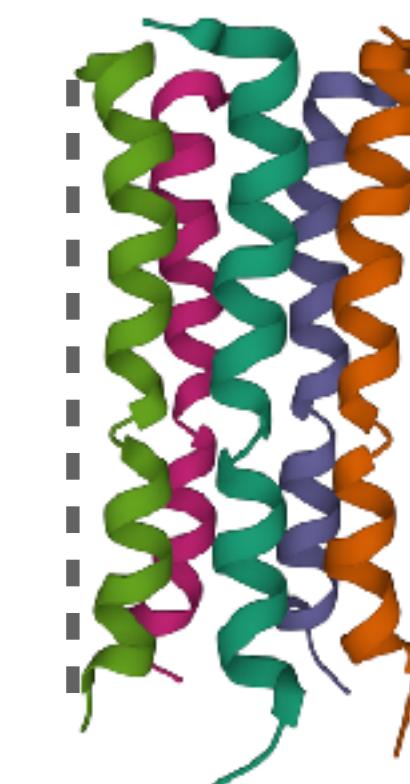
Complete protein



PDB ID: 5X29

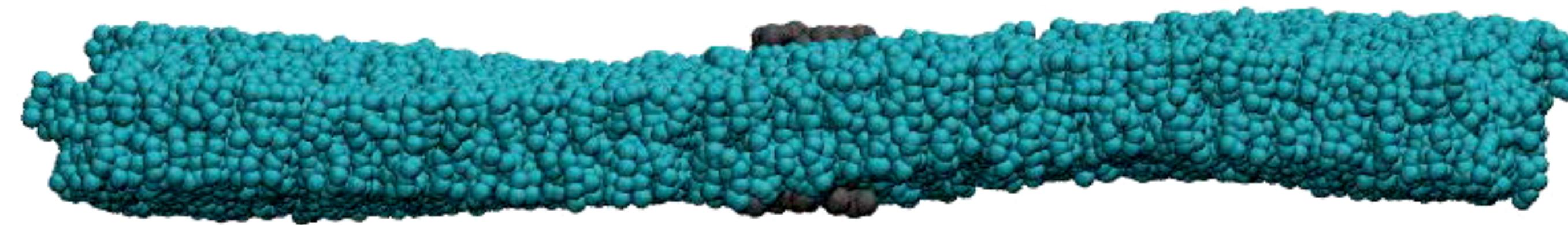


Protein ECD not resolved



PDB ID: 7K3G

Bending still happens, but in opposite direction



Nothing in the literature has an explanation for this!!!

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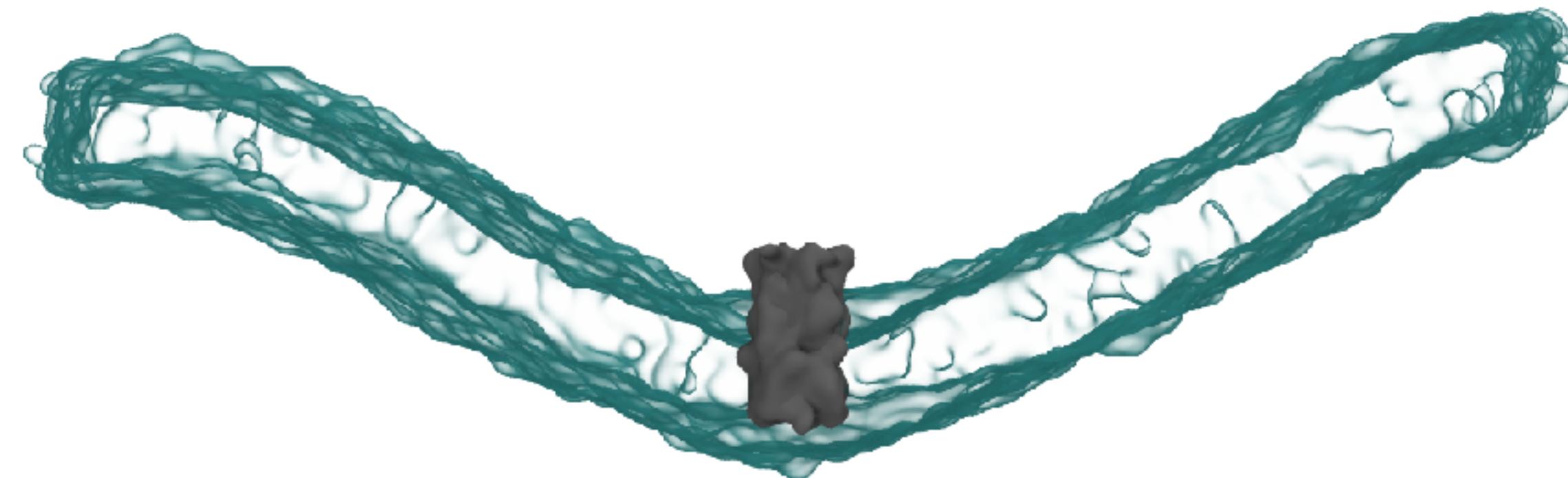
No, but the TMD is doing something completely bizarre

Conclusions

- We can replicate the bending
- The bending gets larger in larger box sizes
- Hydrophobic mismatch seems to explain the local deformations around the protein, but not the large-scale bending we see
- The only way we have been able to remove the bending is by making the membrane stiffer (saturated)
- It isn't a contact angle mechanism
- There is no explanation for the membrane bending we see around the uncapped E protein

Immediate Next Steps

- Something about the TMD of E perturbs local lipids enough to cause bending.
 - Is this a sequence dependent effect?
 - Consider mutating certain AA residues to see if that changes bending signal



Thank You!

Brannigan Lab Members

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Questions?