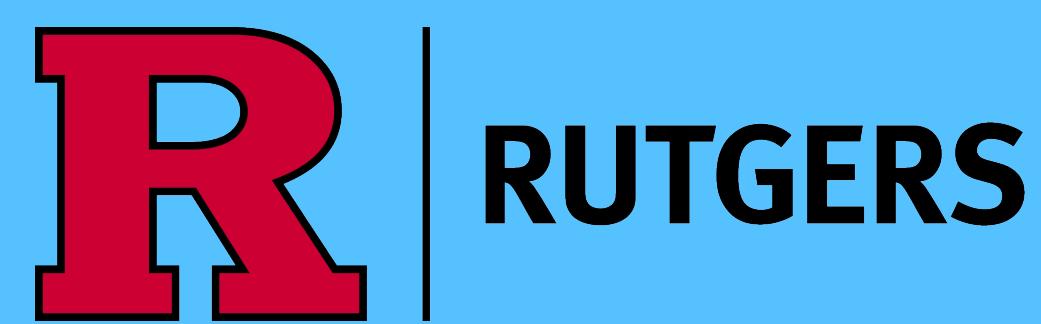
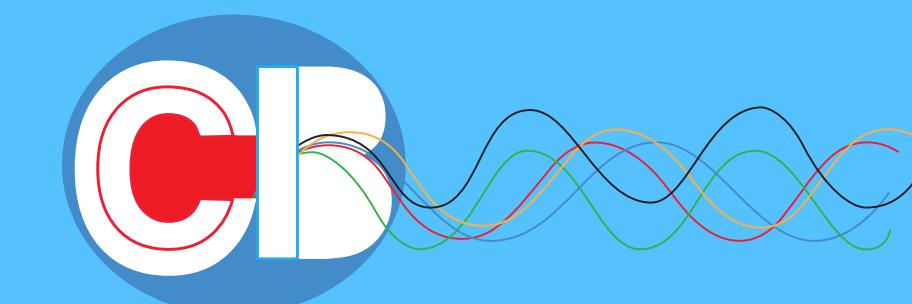


Investigating Membrane Deformations Caused by the SARS-CoV-2 E Protein

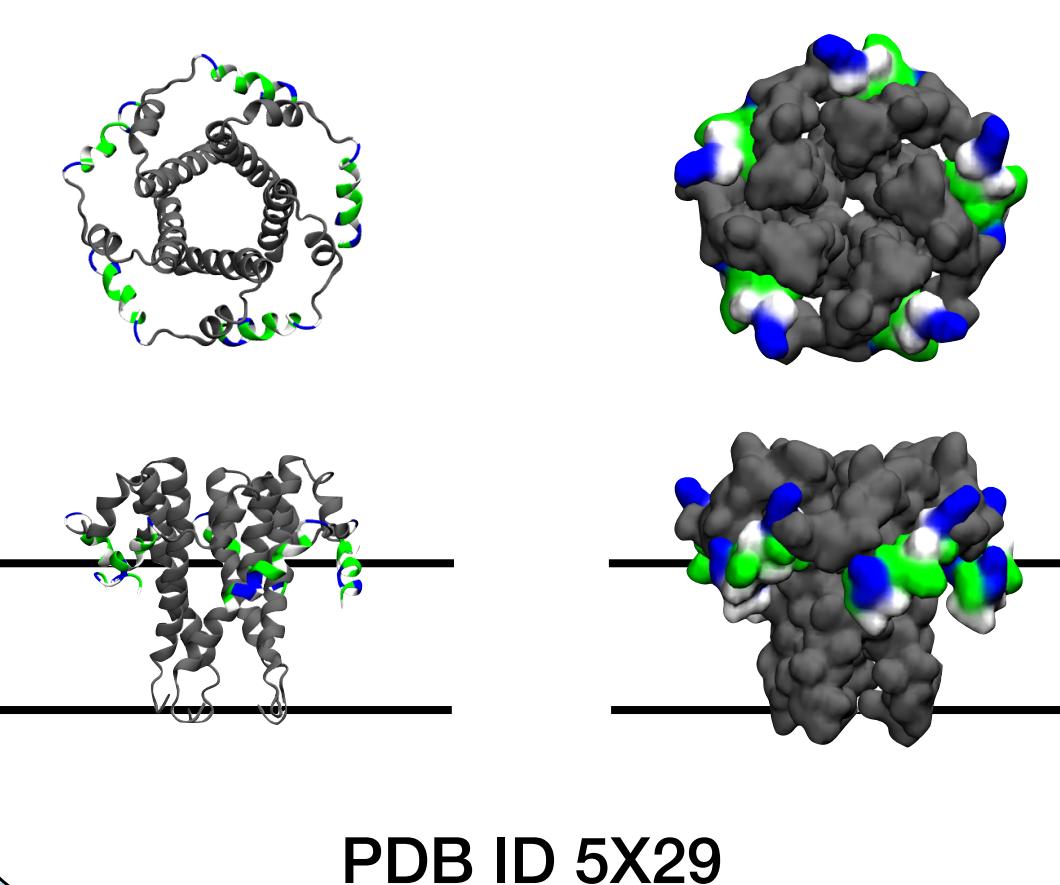


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The envelope (E) protein

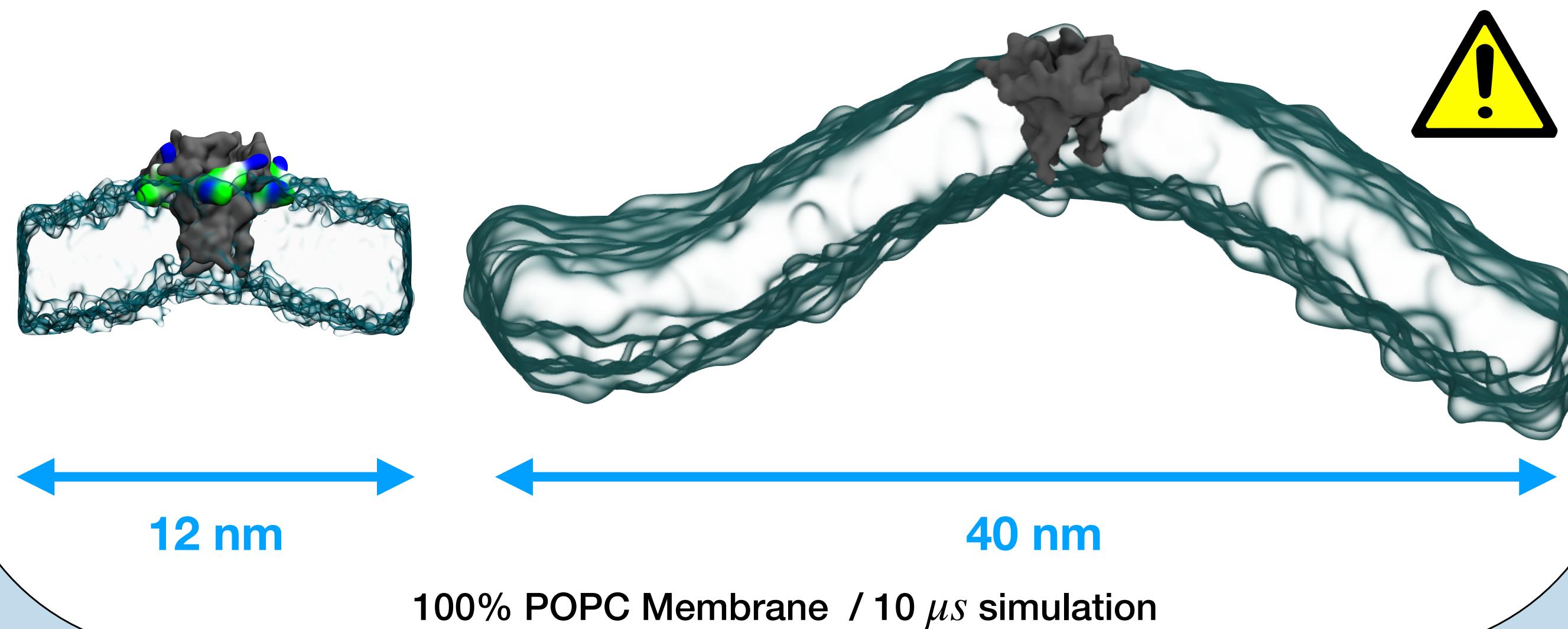


- Pentameric, weakly-selective ion channel
- Highly conserved across many coronaviruses, including SARS-CoV and SARS-CoV-2¹
- Primarily found in the ER-Golgi Intermediate Complex (ERGIC) of infected host cells
- Known to induce membrane curvature, allowing a new virion to bud out and escape the host cell²
- Knock-out or mutation produces weakened virions that are misshapen³ and unable to infect new cells²

Approach

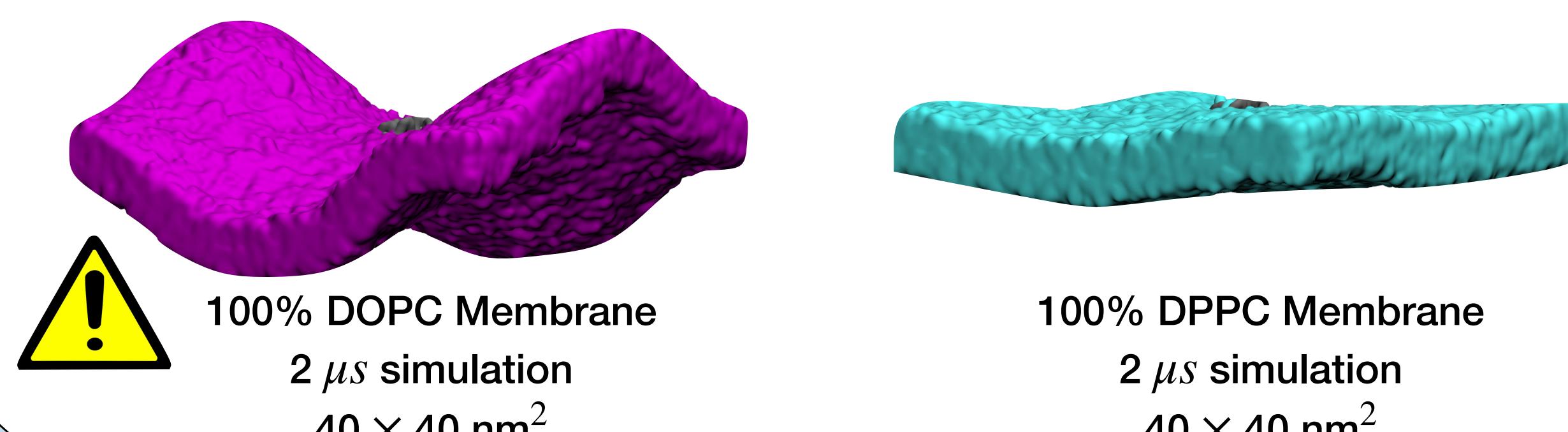
- Simulate with GROMACS 2021 and MARTINI 2.2
- Vary lipid length and flexibility
- Quantify leaflet deformations with *nougat*
- Perform Monte Carlo continuum simulation to compare MD results with elastic theory

E Protein causes membrane bending that increases with system size in CG-MD simulations



Initial observations:

100% unsaturated membranes bend
100% saturated membranes do not bend



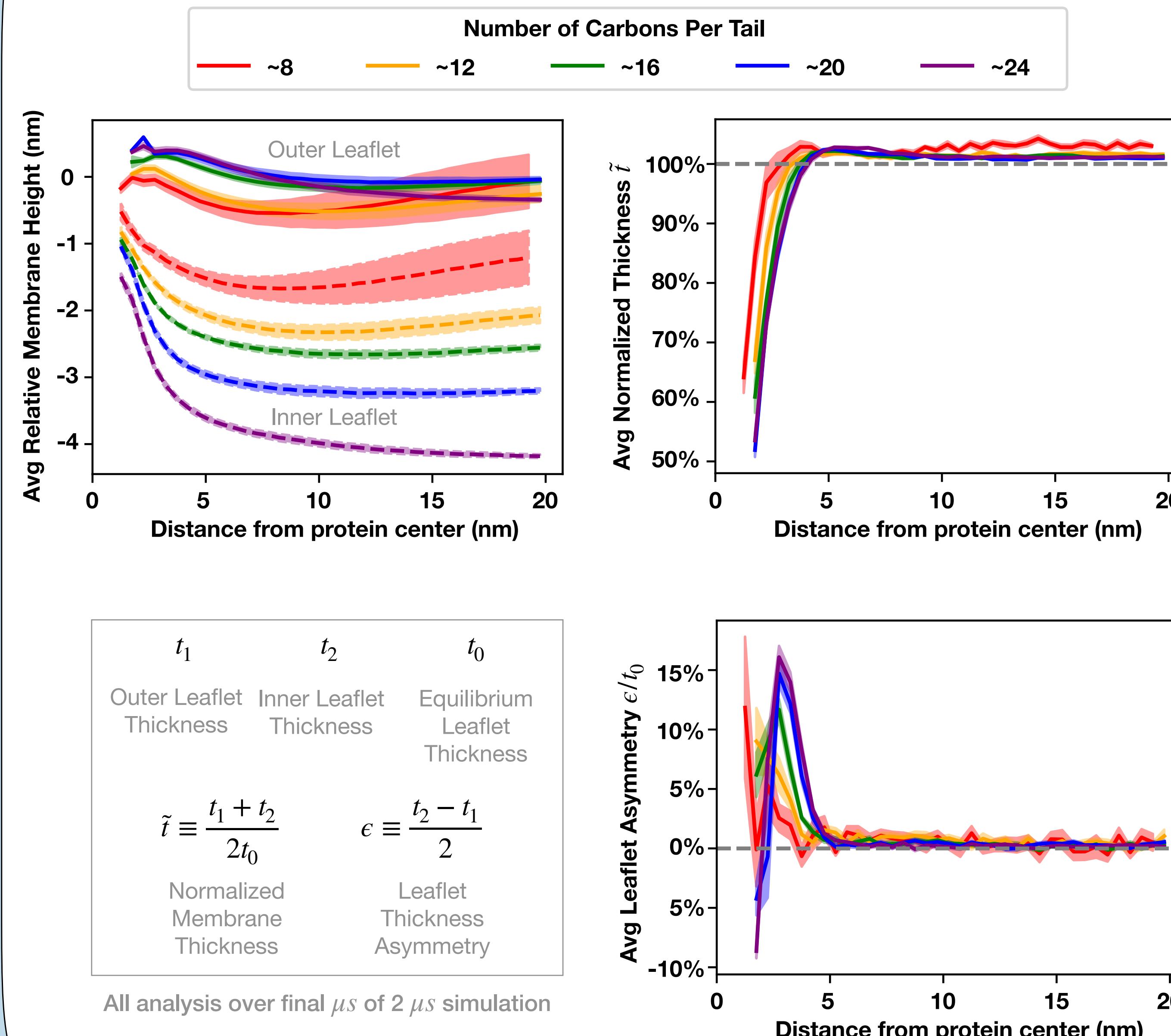
Acknowledgments & Funding

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Rutgers Office of Advanced Research Computing (OARC)

Local asymmetric thickness deformations in saturated systems

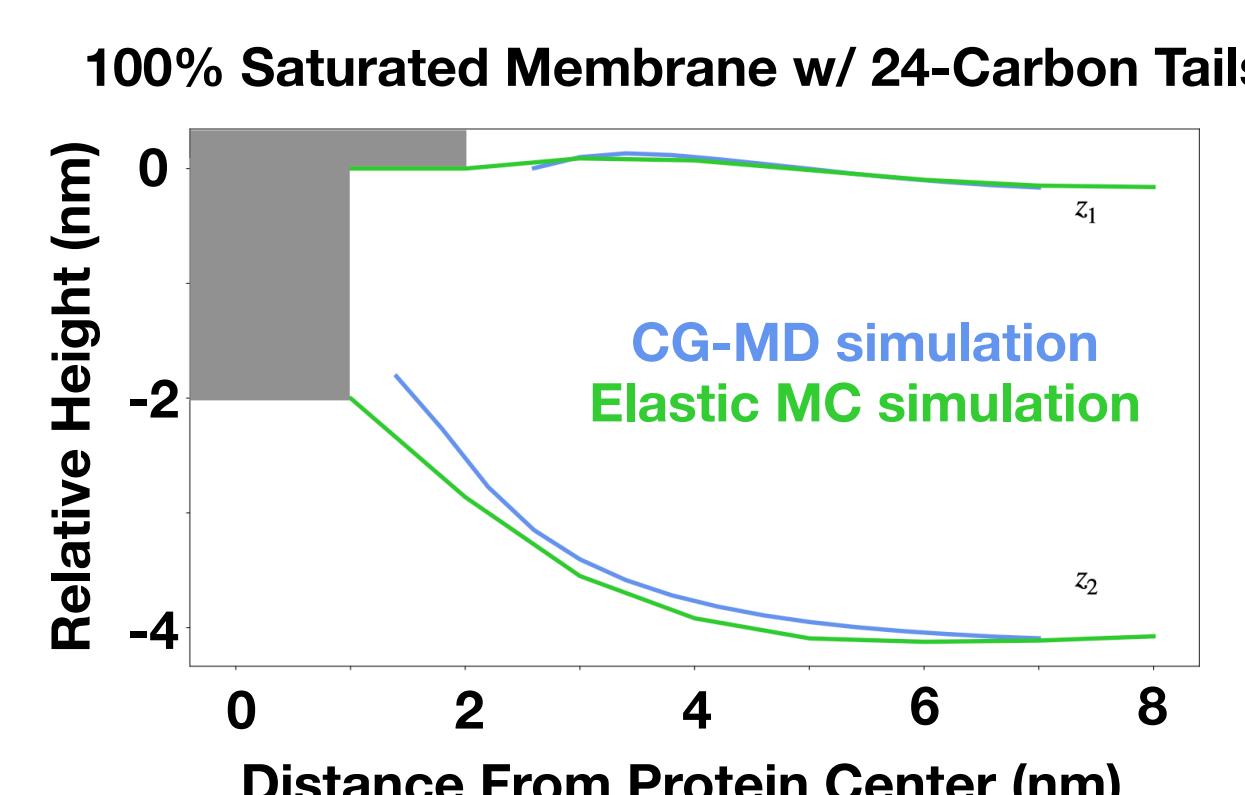


Continuum free energy expression only describes local (saturated) deformations

To account for the asymmetric thickness deviations close to the protein, we revised an earlier expression [4] for the bending energy of the membrane to allow for local leaflet asymmetry ϵ .

$$f_z = \dots + \frac{2\zeta K_C e H^+}{t_0} + \frac{K_A \epsilon^2}{2t_0^2}$$

| | | | |
|----------------|----------------------------------|--------------------------|------------------------------|
| H^+ | ζ | K_C | K_A |
| Mean Curvature | Normalized spontaneous curvature | Bending rigidity modulus | Area compressibility modulus |

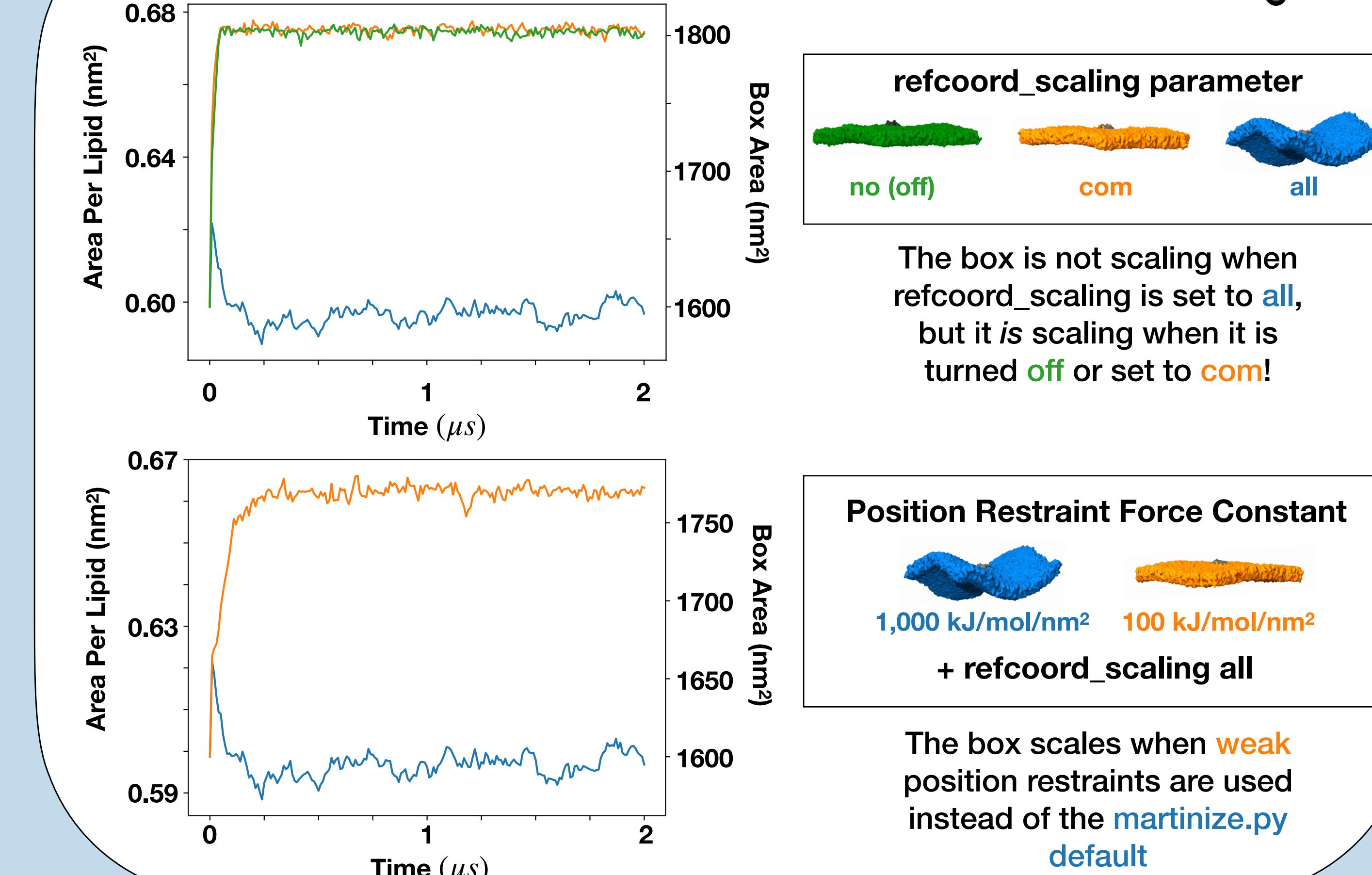


References

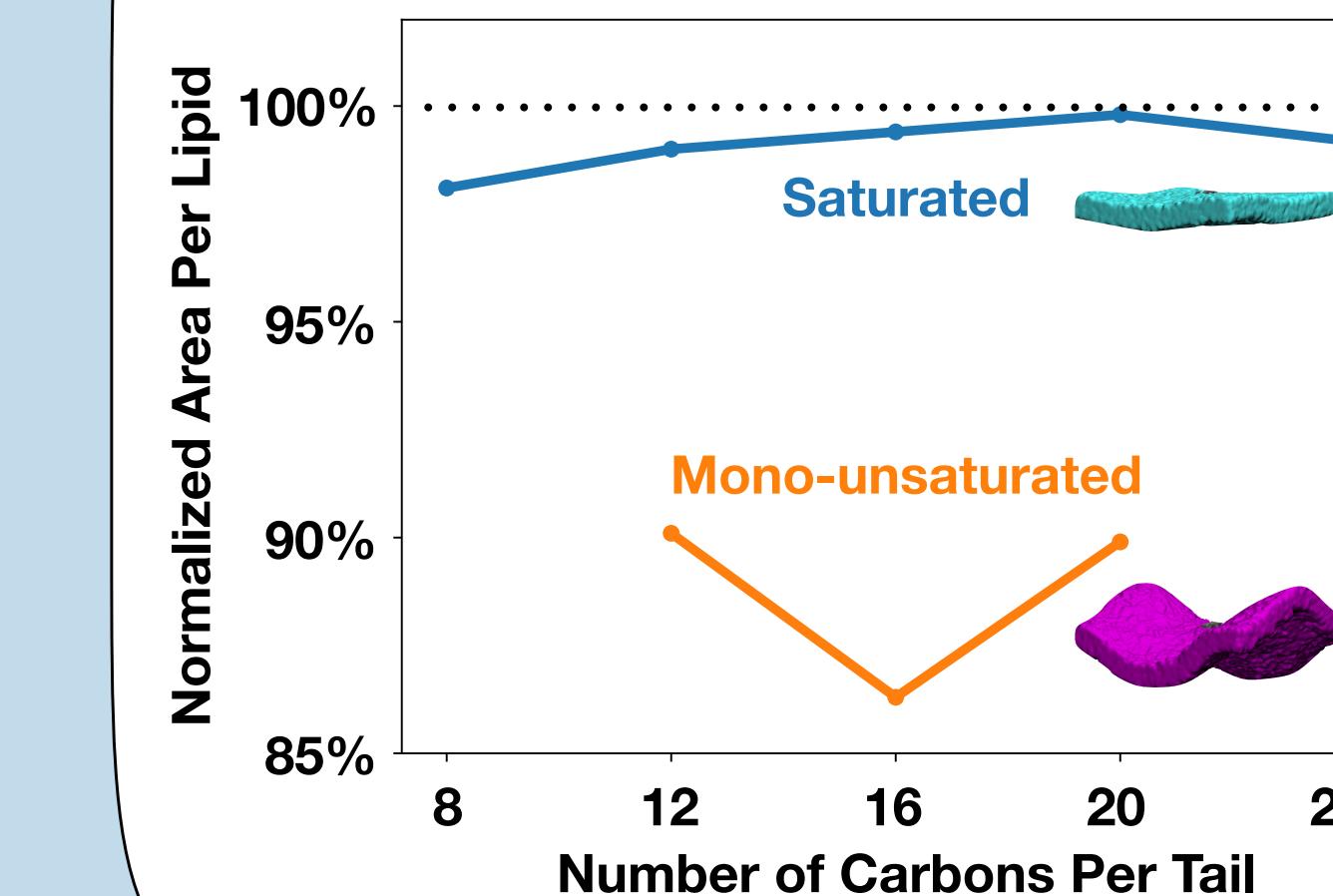
1. Rahman, et al. Gene Reports, 2021
2. Schoeman & Fielding, Virology, 2019

3. Fischer, et al. Journal of Virology, 1998
4. Brannigan & Brown, Biophysical Journal, 2006

Unexpected barostat failure



100% Mono-unsaturated membranes bend due to compression



We ran simulations of the same size with no protein present for 2 μs in order to measure the equilibrium area per lipid for each membrane type

We divided the area per lipid at 2 μs in our protein simulations by the equilibrium area per lipid to get the normalized area per lipid (left)

Mono-unsaturated lipids are compressed when the box is unable to scale, causing the bending response in our simulations.

Conclusions

- The E protein induces asymmetric thickness deformations in 100% saturated membranes
- These deformations are well-described by continuum-level free energy expressions, provided leaflets are allowed to fluctuate independently of one another
- Large-scale bending appears to be a simulation artifact due to an unexpectedly compressed box area
- “refcoord_scaling all” is not behaving as expected in GROMACS (all versions; all semi-isotropic barostats)

Try nougat!

