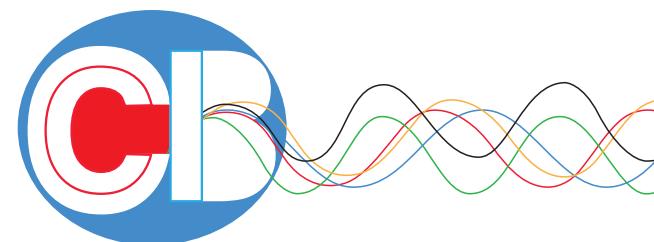


nougat: A Toolkit For Analysis of Membrane Disruption by Proteins and Other Inclusions



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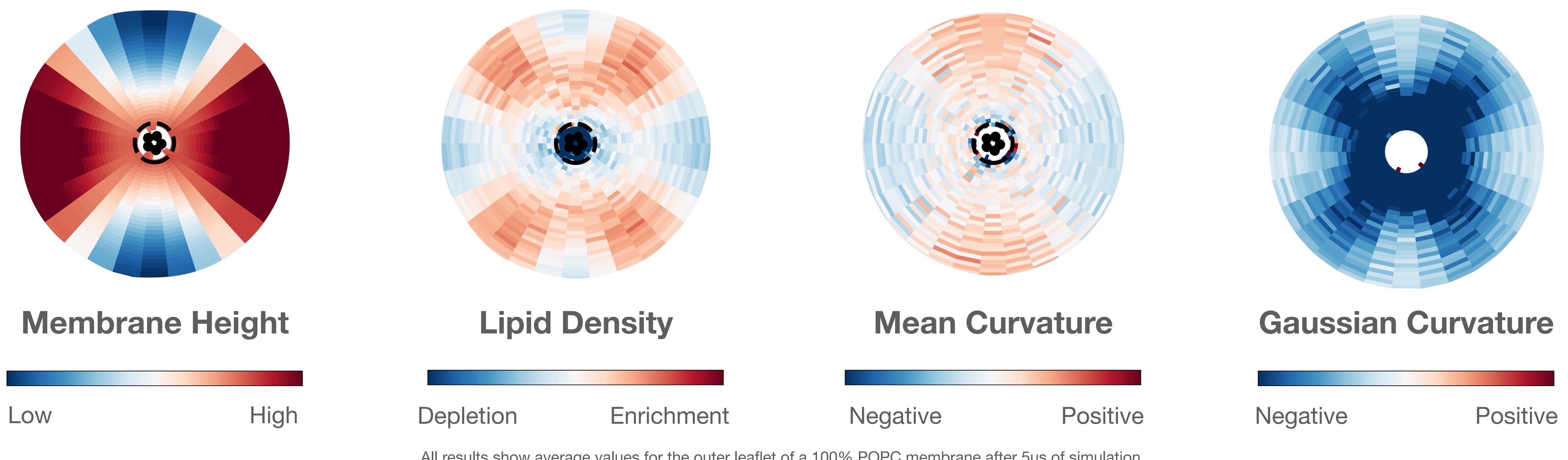


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Abstract

Ion channels are known to interact with membrane lipids in numerous ways, including through the differential recruitment of particular lipid species, local realignment of lipid tails, and even inducing comparatively long-range deformations of the membrane surface. Coarse Grain Molecular Dynamics (CG-MD) simulations offer an attractive ‘computational microscope’ through which to observe these phenomena. While some packages do exist for the analysis of lipid binding, we are not aware of any that offer a holistic view of protein-membrane interactions. We introduce *nougat*, a toolkit for quantitative analysis of several measures of interest local to a membrane protein: membrane thickness, membrane curvature, lipid density, and lipid tilt. We demonstrate the tool using the Envelope (E) protein from SARS-CoV – a pentameric viroporin known to induce membrane curvature in order to initiate the budding process and allow a new virion to escape its host cell.

Quantitatively Measure Membrane Deformation Over Trajectory



SARS-CoV E Protein

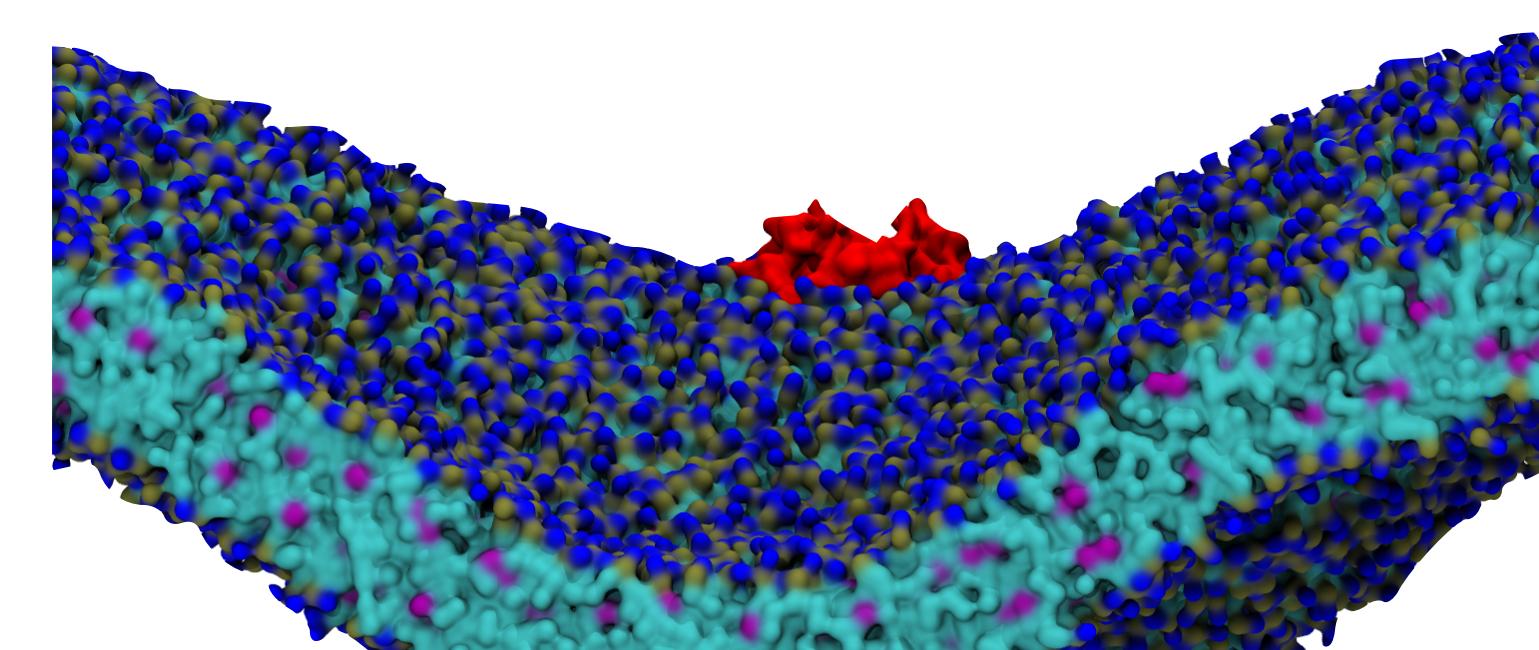


Top-down (top) and side (bottom) views of the pentameric structure of the SARS-CoV E protein (PDB ID 5x29). Certain residues are colored to illustrate the five-fold symmetry of the protein. Black bars illustrate approximate location of membrane leaflets.

- Oligomerizes to form pentameric ion channel
- High rate of expression in host cell ERGIC
- Induces membrane curvature in order to initiate the budding process
- Curvature induction mechanism unidentified to date

Motivation

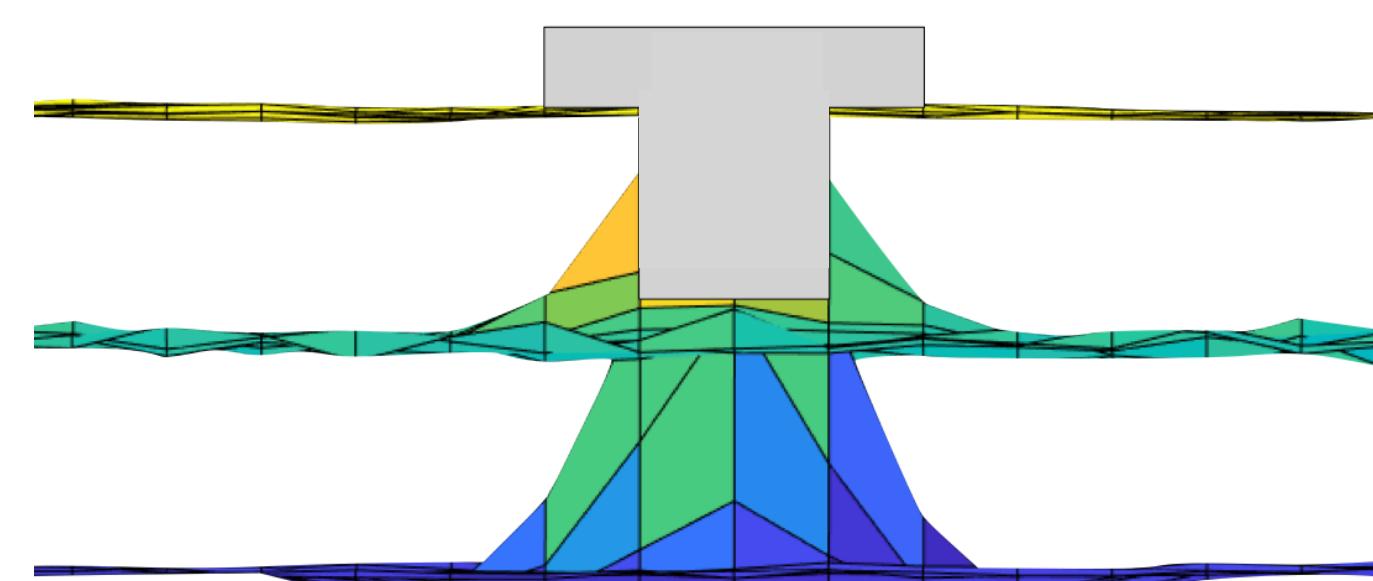
- The SARS-CoV E protein is 94.8% identical and 96.1% similar to the SARS-CoV-2 E protein¹
- E protein knockout in related coronaviruses has drastically altered virus’ envelope shape and ability to infect new cells²
- Understanding how E participates in the budding process could aid in halting the spread of Covid-19
- Identification of E protein’s curvature induction mechanism requires the quantitative comparison of membrane properties in many different simulation systems



Still image taken from CG-MD simulation of E protein in 100% POPC membrane. The membrane has adopted a clear saddle-shaped deformation local to the protein.

Explore the Membrane-Inclusion Interface in 3D

Continuum Model



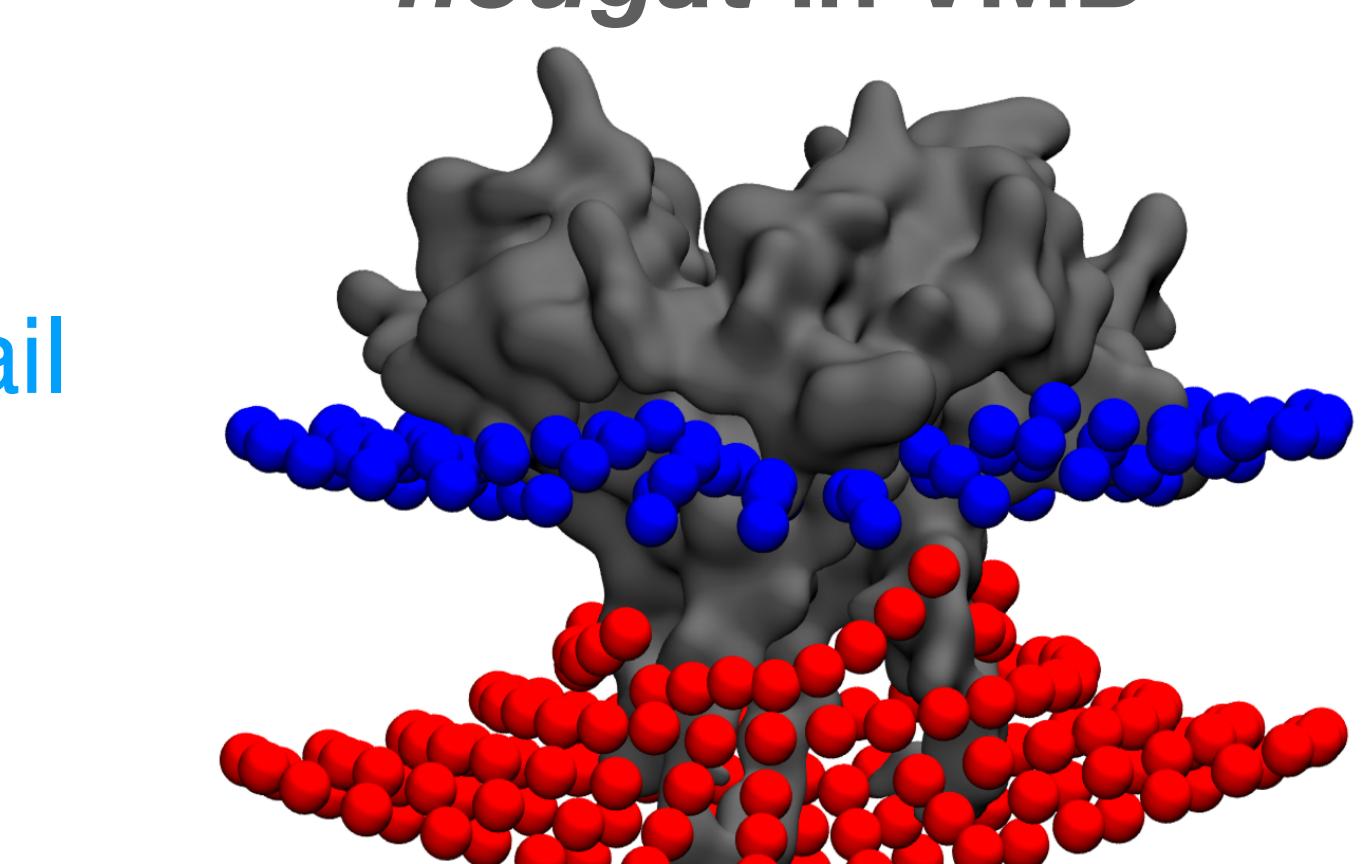
Snapshot taken after 100 steps of a continuum monte carlo simulation. E protein is modeled as two cylinders (grey). The outer leaflet is pinned to the underside of the upper cylinder, mimicking the effect E protein’s cap may have on the membrane.

In addition to providing .dat and .png output files, *nougat*:

- Creates a PDB file that allows you to examine the average membrane surfaces in VMD
- Imports additional data into user fields, allowing for coloring by density, mean curvature, and gaussian curvature
- Performs analysis on every bead in the lipid tail, allowing for the exploration of local compression effects
- Draws arrows to show average lipid tail vector, surface normal, and lipid tilt

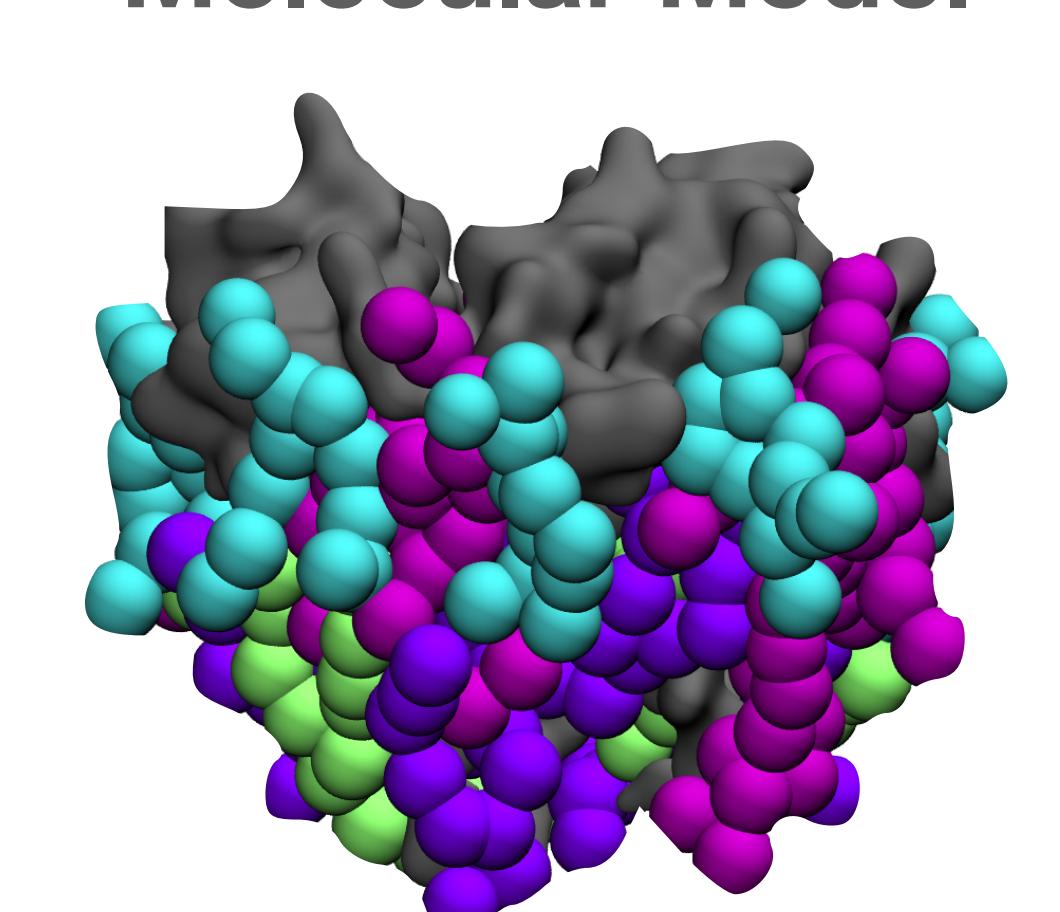
This has facilitated comparisons not just across simulation systems, but also with continuum models that predict membrane deformations around inclusions. The results from *nougat* are currently being used to inform revisions to our continuum model, which will in turn identify E’s curvature mechanism.

nougat in VMD



Results from *nougat* analysis imported into VMD with PDB-maker feature. Average positions of the outer (blue) and inner (red) leaflets within 5 lipidation shells are displayed.

Molecular Model



POPC lipids colored by resid within 5 angstroms of the protein backbone.

Other *nougat* Features Coming Soon

June Update

- Lipid tail vectors
- Surface normal vectors
- Lipid tilt vectors
- Membrane thickness
- Allow for heterogeneous systems

July Update

- Allow for multiple inclusions
- Allow for analysis of AA simulation systems
- Lipid tail order

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- CAREERS Cyberteam

References

1. Rahman et al. Gene Reports, 2021
2. Fischer et al. Journal of Virology, 1998

Try Me!

