Construction of a Continuum Elastic Simulation Pipeline for Prediction of Protein-Induced Membrane Deformations

Launch Presentation

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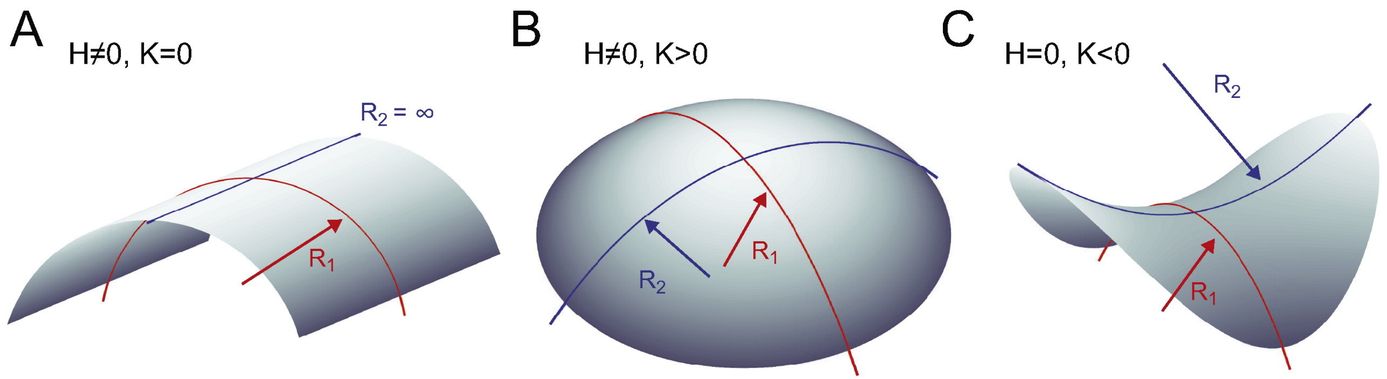
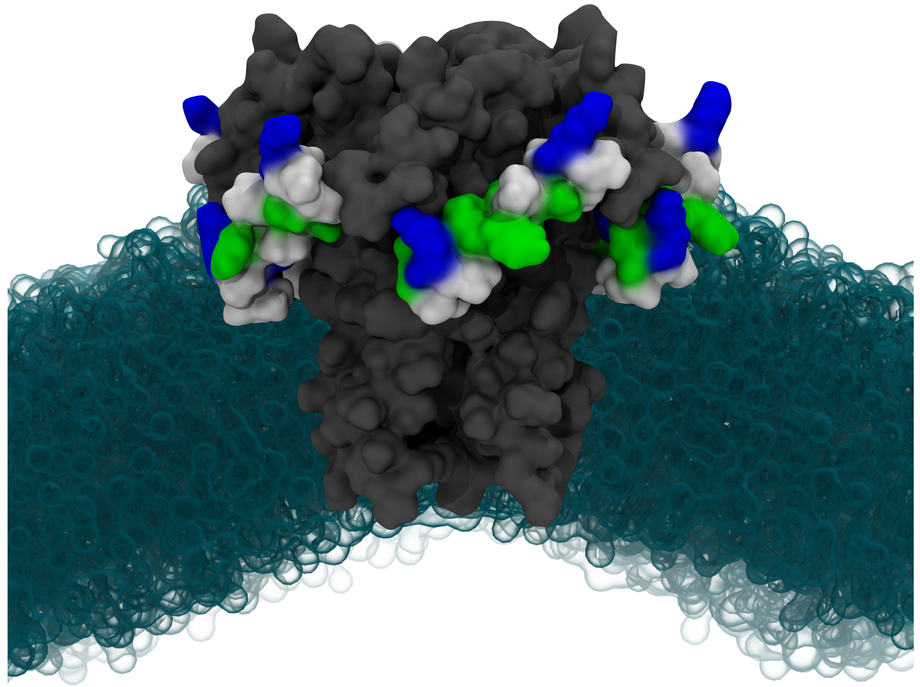


Argudo, et al. Biochim. Biophys. Acta, 2016

Motivation: Continuation of Covid-19 research

- Envelope (E) Protein is known to induce membrane curvature; aids in virus budding and escape of host cell
- Mechanism behind induction of curvature is unknown at this time
- The Brannigan lab has collected evidence through Coarse-Grain Molecular Dynamics (CG-MD) simulation that suggests the mechanism is related to shape of E protein (shortened TMD with large inflexible protein ‘cap’)
- To confirm this “Asymmetric Hydrophobic Mismatch” mechanism, the lab needs to create elastic simulation code for the analysis of membrane deformation by irregularly-shaped protein inclusions like the E protein



How This Type of Simulation Works

- Input membrane constraints based on protein shape
- Repeatedly perturb membrane height at random locations on lattice
- Metropolis Monte Carlo protocol using bending energy as acceptance weight guides simulation to sample lowest energy membrane conformations
- Researcher can then compare against CG-MD conformations for verification of hypothesis

Motivation: Prediction of Membrane Deformation

- Proteins can cause significant membrane deformation
- All-Atomistic Molecular Dynamics (AA-MD) simulations occur over timescales that are too short to allow membranes to relax into (deformed) lowest energy conformations
- This frustration could affect how the protein and membrane behave in AA-MD simulation
- Using a continuum elastic simulation to predict the lowest energy membrane conformation and using that information as a starting point for an AA-MD simulation could be enormously beneficial

Why an RCF is needed

- The Brannigan lab has a codebase that does this, but it is written in C (no built-in parallelization), assumes a symmetric protein inclusion, and simulates a monolayer
- The RCF will need to:
  - Write an input generation script that will output membrane constraints for any irregular protein inclusion (not just E protein!)
  - Write Metropolis Monte Carlo and bending energy analysis scripts that make use of MATLAB parallelization commands
  - Extend the codebase so that lipid bilayers can be analyzed
  - Create documentation for the above so that group members can implement on their own proteins of interest using Rutgers high-performance compute cluster

Project Stages

- Familiarization (1 month)
    - Verify earlier experimental findings with additional MD simulations (complete)
    - Read about bending energy, Metropolis Monte Carlo, etc… (complete)
    - Comment C code and use as a knowledge check with the researcher (current)
- Coding Stage I (1 month)
    - Use MATLAB to recreate continuum elastic simulation of symmetric inclusion and monolayer with parallelization
- Coding Stage II (3 months)
    - Write code that can generate input constraints from any protein TMD
    - Generalize Stage I codebase to include second leaflet and irregular inclusions
- Documentation (1 month)
    - Write documentation for both tools (input generator and simulation)
    - Write documentation for their use on Rutgers high-performance compute resources

What I Expect to Learn

- MATLAB & C
- Strategies for efficient parallelization of algorithms
- How to measure curvature & bending energy
- How Metropolis Monte Carlo works
- How to create useable documentation

Goals for Next Month

- Comment C code for review by researcher
- Recreate C simulation in MATLAB
- Fully understand the concepts behind the measurement

Help Needed

- A MATLAB syntax tutorial for people who already know how to code