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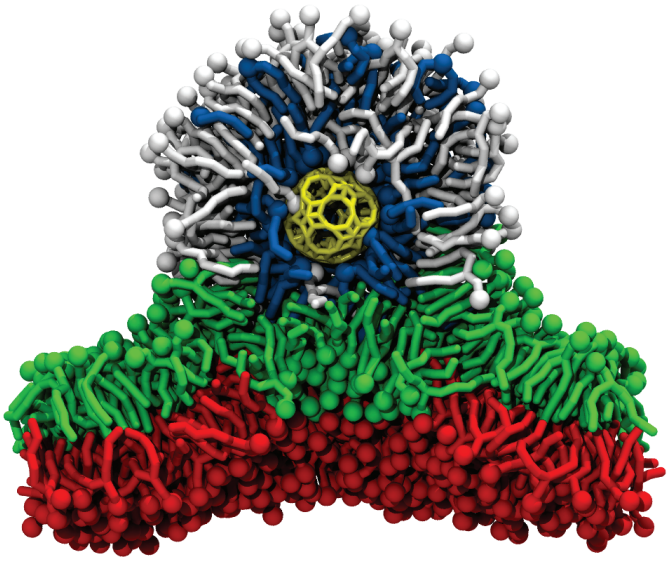
Modeling Synthetic Ion Channels with MD



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1 Introduction

In this tutorial, we will recreate the study, "Synthetic Ion Channels via Self-Assembly: a Route for Embedding Porous Polyoxometalate Nanocapsules in Lipid Bilayer Membranes" [1], to demonstrate how one designs and implements a research project using molecular dynamics (MD) as a tool. The researcher will learn to create and visualize systems in Visual Molecular Dynamics (VMD) [2] using the TCL interface, create coarse-grain models of biological and metallic molecules and perform MD simulations with NAMD [3], an MD package developed here at the University of Illinois.

The motivation for this research project stemmed from the discovery of polyoxomolybdates (POMs) which form porous nanocapsules [5, 6, 7, 8] made of twelve pentagonal molybdenum oxide regions:

$$[(\text{Pentagon})_{12}(\text{Linker})_{30}]^{72-} \equiv [\{(\text{Mo})\text{Mo}_5\text{O}_{21}(\text{H}_2\text{O})_6\}_{12}\{\text{Mo}_2\text{O}_4(\text{SO}_4)\}_{30}]^{72-}.$$

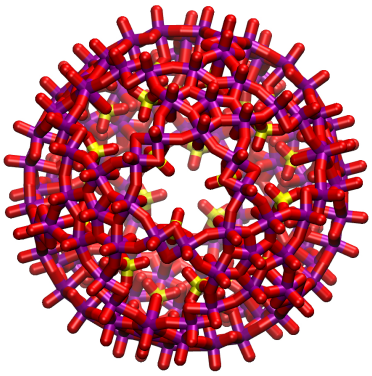

Figure 1: All-atom structure of the capsule, oriented with a pore in the center. Three sulfate groups line each pore, forming a triangle with sides of 5.6 Å [4]. Molybdenum atoms are shown in purple, oxygen in red and sulphur in yellow.

The connection of the 12 pentagonal units forms 20 circular pores on the surface of the capsule, shown in Fig. 1. Previous studies have shown that water and small inorganic cations can enter the capsule cavity through the pores [5, 4, 9]. Moreover, it has been shown that the selectivity of ion transport through the nanocapsule can be customized, and the pores themselves can be reversibly blocked [5, 10, 4]. Thus, it appears that the porous nanocapsules can serve as models of biological ion channels, whose structure can be engineered at the atomic level. To fully reproduce typical physiological conditions, a porous nanocapsule would, ideally, be placed in a lipid bilayer membrane. However, the nonpolar, hydrophobic interior of the lipid bilayer membrane is not compatible with the high charge of the capsule.

In this tutorial, we will set up, perform and analyze MD simulations demonstrating a route for embedding POM porous nanocapsules in lipid bilayer membranes via self-assembly. It is known that these porous POM nanocapsules can be encapsulated with dimethyldioctadecylammonium (DODA) surfactants, amphiphilic cations consisting of a cationic ammonium group attached to two long nonpolar tails [11, 7]. Here, we will design and implement a research project to show that the DODA–capsule interaction can be exploited to create a liposome-like, water soluble structure that can fuse with a lipid bilayer membrane and thereby embed a POM porous nanocapsule in the bilayer.

2 Creating a Model of the POM Nanocapsule

Before we can outline a strategy for our research project, we first need a good model for the POM nanocapsules. In this section, we will investigate the struc-

ture of the POM nanocapsules and create a coarse-grained model of the nanocapsules that we can use in MD simulations.

2.1 Examining the Structure

Before we create a detailed model of the POM nanocapsule, let's first look at the all-atom structure of the capsule. For this, we will use VMD through its TCL interface.

1. VMD comes with a convenient console plugin called TK Console. To open the tcl console, start a new VMD session and click on Extensions → Tk Console.

2. We must first move to the directory that we are working in. To do so, enter the following in the console:
   `cd Path_To_Tutorials/POM_Nanocapsule_Tutorial`
   (All tcl code will be shown in this typeface.)

3. Next, let's load the structure of the POM nanocapsule. The structure we have has been provided by our collaborators, who solved the structure with X-ray crystallography.
   `mol new Structures/CapsidAllAtom.pdb`
   Now we have loaded a "PDB" file, or Protein Data Bank file, which contains the locations of the atoms. While this file type has the word "protein" in the title, in practice, it is used for any sort of molecule. This PDB was given to us by an experimental group, so it also contains information on the connectivity, which is usually not in a PDB.

4. When a system is loaded, VMD will use a very simple representation. Here we see that the capsule is initially sketched out in the "line" representation.

   Open the Graphical Representations toolbox through Graphics → Representations. In the Drawing Method dropdown menu, select Licorice.

   What we see here is everything that was solved with X-ray crystallography: the POM capsule and the surrounding structured water. To view only the capsule, change the Selected Atoms to `element Mo O S and within 3.5 of element Mo S`.

   Now we can see the macromolecular structure we are working with. Identify the Molybdenum atoms, the Sulfur atoms and the Oxygen atoms. The charge on the capsule is located in the molybdenum oxide pentagonal units.

   Here are somethings to think about:

   (a) Where would ions enter the capsule?

(b) How can the structure of the capsule be altered to change ion selectivity?

2.2 Choosing a Model for the POM Nanocapsule

In order to simulate the POM nanocapsules in solution with DODA and lipids, we need a model for the kinetics of the molecule. The structure we have for the POM capsule is in all-atom detail. Normally, MD simulations of biological molecules, such as proteins, are performed to all-atom detail, because the dynamics of the molecules are affected by atomic details (think of the hydrogen-bonding in DNA). However, simulating a molecule at the all-atom level requires an equally-precise description of the dynamics.

For all-atom molecular dynamics, we use the potential energy function

$$\begin{aligned} U_{\text{all atom}} &= \sum_{\text{bonds } i} k_i^{\text{bond}} \left(r_i - r_{0i}\right)^2 + \sum_{\text{angle } i} k_i^{\text{angle}} \left(\theta_i - \theta_{0i}\right)^2 \\ &\quad + \sum_{\text{dihedrals } i} k_i^{\text{dihed}} \begin{cases} \left[1 + \cos\left(n_i\phi_i - \gamma_i\right)\right] & n_i \neq 0 \\ \left(\phi_i - \gamma_i\right)^2 & n_i = 0 \end{cases} \\ &\quad + \sum_i \sum_{j>i} 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j>i} \frac{q_i q_j}{4\pi\epsilon r_{ij}}, \end{aligned}$$

where the force, $\vec{F}$, is given by $-\vec{\nabla}U$. The charges q_i are calculated relative to the water model used — in our case, TIP3P (a three point water model). Currently, there is no description of molybdenum oxides at this level of detail compatible with our model. Such a description requires lengthy and difficult quantum calculations which need to be reconciled with experimental results. For a description of ionic transport through a nanocapsule, such a description would be necessary. However, for our current project, such a fine level of detail is unnecessary.

For the current project, we will use coarse-grain molecular dynamics (otherwise known as CGMD). In CGMD, atoms are replaced by beads, which represent groups of atoms (for lipid models, usually 4 atoms per bead). For example, a water molecule would be represented by one "water" bead, and a amino acid in a protein by two beads — a "backbone" bead and a "sidechain" bead. In CGMD, the beads interact with each other much like atoms do in all-atom MD, except the interactions are restricted to short ranges and there are only a handful of different types of beads (compared to all-atom molecular dynamics, where there are many different types of carbon, for example). The simplification of the potential and the reduction in the number of atoms also makes CGMD much faster than MD — people have reported a speed up of up to 1000 times [12].

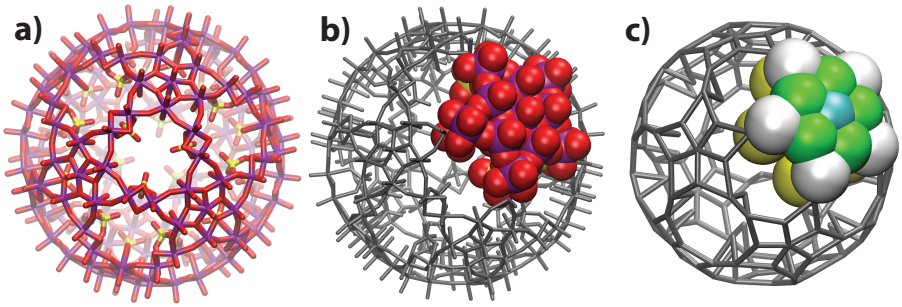

Figure 2: The POM nanocapsule. a) All-atom structure of the capsule, oriented with a pore in the center. Three sulfate groups line each pore, forming a triangle with sides of 5.6 Å [4]. Molybdenum atoms are shown in purple, oxygen in red and sulphur in yellow. b-c) Mapping from the All-atom (b) to the CG (c) model of the porous nanocapsule. The capsule considered here is made of 12 repeats of a pentagonal unit. Thus, specifying the mapping of one all-atom pentagonal unit and its linker units to the CG representation is sufficient to describe the mapping of the entire capsule. The colors in the CG representation highlight the four different types of beads used to model the capsule.

2.3 Coarse-Grain Model of the Capsule

Fig. 2 details the coarse-graining procedure for the POM nanocapsule. One bead in the coarse-grain model represents groups of molybdenum and oxygen or oxygen and sulfur atoms. Even though the coarse-grain description is much simpler than the all-atom description, we are still lacking a dynamical description of the POM nanocapsule. To overcome this, we will simulate the capsule with strong bonds and angles to keep the capsule rigid.

Now let's take a look at this model in VMD.

1. Load the molecule:
   ```
   mol new Structures/CapsidCoarseGrain.psf
   mol addfile Structures/CapsidCoarseGrain.pdb
   ```
   The "PSF" file, or Protein Structure File, contains the atom connectivity (bonds, angles, dihedrals) as well as information necessary to use the system in MD simulations.

2. View it in `Licorice` or `vdW`. Color it by `Type`.

3. Compare it to the all-atom structure of the POM nanocapsule. What are the main features of our coarse model?

3 Encapsulation of the POM Nanocapsule

In order to place the POM nanocapsule into a lipid bilayer membrane, the capsule must first be neutralized. It has been shown that these porous POM nanocapsules can be encapsulated and neutralized with a surfactant, dimethyldioctadecylammonium (DODA). DODA molecules are amphiphilic cations consisting of a cationic ammonium group attached to two long nonpolar tails [11, 7]. To test our model, we will simulate the POM nanocapsule in a solution of DODA and see if we can replicate the experimental results.

3.1 Modeling the Surfactant

Before we can simulate the nanocapsule with DODA, we must first create a CG model for it.

1. Find the chemical structure for DODA online. What does this chemical look like?

2. How would you coarse grain this consistent with our CG model? We typically choose four atoms per bead when we coarse grain lipid-like molecules. When we coarse grain, we can make beads charged, polar or apolar (with variations like hydrogen-bonding).

3. Let's take a look at the coarse-grain model of DODA.
   `mol new Structures/DODA.psf`
   `mol addfile Structures/DODA.pdb`

4. Using the representations and coloring available in VMD, locate the charge on the molecule. How does the coarse-grain representation compare to the all-atom model? Were you correct in how to model it?

3.2 Create the simulation system

Now we are ready to perform some simple simulations. Let's make our simulation systems. To test our model, we will simulate the nanocapsule in hexane, surrounded by DODA.

1. Change directories into the `3.DODA/` directory.
   `cd 3.DODA/`
   (type this in the tkCon and in the shell.)

2. We are making a system with the POM nanocapsule at the center, surrounded by DODA and hexane. The first thing we want to do is distribute the DODA in a box around the nanocapsule. To make a distribution of

DODA, we will use VMD. VMD has a scripting interface which uses the TCL scripting language.

Open the `make_DODA_box.tcl` file in emacs (or your favorite editor, if you have one).
`emacs make_DODA_box.tcl`
Now, read through the file, and identify what the script does.

3. Run the TCL code in VMD. On the command line, type
`vmd -dispdev text -e make_DODA_box.tcl >output.DODA`

4. Look at the output and match the output to the commands in the TCL file. To view the output, open it in emacs, or use less.
`less output.DODA`

5. Now look at the .pdb and .psf file you created in VMD. When you make a system, it's always good to check that you made the system that you thought you did.
`mol new DODA_box.psf`
`mol addfile DODA_box.pdb`

6. Now we want to make a box of Octane. We can modify the `make_DODA_box.tcl` script to do this. Make the new script by typing
`cp make_DODA_box.tcl make_Octane_box.tcl`
in the command line.

   Open the new script in emacs. Edit it so that it makes a box of octane.

   (a) Change the `outPrefix` to `Octane_Box`.

   (b) Specify the Octane molecule instead of DODA.

   (c) Make the box bigger (100 A instead of 90).

   (d) We want something like 15 times as many octane molecules as DODA molecules.

   (e) Change the segname to OCT

   (f) Change the topology command to use the octane topology file.

7. Now, run this script and check the output to make sure there were no errors.

8. We have a box of octane and a box of DODA. We want to combine them with the POM nanocapsule to make our system. The script `make_nonpolar_system.tcl` does just this. Open the file and see what it does. Run it on the command line with VMD. Check to make sure there weren't any errors, then look at the system in VMD. You just made your first simulation system!

3.3 Simulating the systems

Now that we have made our POM Nanocapsule / DODA / Octane system, we are ready to simulate it with NAMD.

1. When we run NAMD, we need to tell it what we want it to do, so we give it a config file. Let's take a look at the NAMD config file we're going to use here. On the command line, open the file.
   `emacs Equilibrate_Nanocapsule_Nonpolar_Solution.namd`

2. Read through the file and figure out what each section does. What is different about our NAMD config now that we are using the CG potential?

3. Run namd, either on the command line or on a local cluster. (If you do not have time to run these simulations, results from a previous simulation are available in `_Good/`.)

4. While you are waiting for the results, you can begin to work on the analysis.

3.4 Analyzing the results

Now we have run a simulation. We need to verify that the simulation was good, and extract same meaningful data from it.

1. Open up the results in VMD. The coordinates were saved every 0.1 ns to a binary file called a DCD file. The DCD file only contains the coordinates, so we also need to load the original PSF file before we can view the simulation.

2. During the course of the simulation, the POM nanocapsule will wander around the simulation box. To get a good visual analysis of the system, it is easiest if we view it in a frame where the center of mass of the POM nanocapsule is still. To do so, type the following into the tcl console:

```
set all [atomselect top all]
set caps [atomselect top "resname CAPS"]
set nf [molinfo top get numframes]

for { set frame 0 } { $frame < $nf } { incr frame } {
$all frame $frame
$caps frame $frame
$all moveby [vecinvert [measure center $caps]]
}
```

Now, the system is centered around the capsule, but the edges of the simulation will bounce around quite a bit. We want to re-wrap the simulation around the simulation cell. In the console, type:
`pbc wrap -all -center centerofmass -centersel "resname CAPS" -compound residue`
Here we use the PBC (periodic boundary conditions) plugin to rewrap our simulation, but to keep molecules intact. (For our analysis later, we will actually break the molecules apart when we wrap them.)

3. Look at the trajectory. What happens? Does it look like the simulation is in equilibrium? Try using different representations to get a better look. (Don't close VMD after this step — we'll come back to this in the next section.)

4. Now we want to do some numerical analysis on the system, to get quantitative results. The first thing we can do is to calculate the number of DODA in direct contact with the POM nanocapsule during the course of the simulation. This will give us an idea of when the simulation approaches a steady state (if it does). In the directory `Analysis`, there is an analysis script which does just this. Read through it and determine what it is doing.
`cd Analysis`
`emacs calculate_number_bound.tcl`
How would you change this to calculate the number of octane molecules near the capsule?

5. Run the script on the command line.
`vmd -dispdev text -e calculate_number_bound.tcl >output.number_bound`

6. View the results in xmgrace, a plotting program.
`xmgrace NumberDODA.dat &`
Does the system approach a steady state?

7. Now let's look at the structure of the POM Nanocapsule–DODA ball. Take a look at the script Radial_Distribution.tcl.
`emacs Radial_Distribution.tcl`
This script will plot the density of the POM Nanocapsule, DODA and octane as a function of radial distance, averaged over each frame. Look through the script and identify what is happening.

8. Let's run the script. But before we do, we need to set the value of `firstFrame` to the first frame we want to start our average over. What makes sense to put here? Make a choice, then run the script.

9. Examine the results in `xmgrace`. What can you say about the structure?

10. What other analysis could we do? If there is time, write a script which plots the total charge as a function of radial distance — is the capsule-DODA ball neutral?

4 Creation of a Functional Liposome

Now that we have shown that our model properly recreates the POM Nanocapsule–DODA interaction seen experimentally, we want to see if we can develop a protocol for inserting the POM-Nanocapsules into lipid bilayer membranes.

4.1 Motivation for the Protocol

1. To insert the POM nanocapsule into a bilayer, we are going to take advantage of the DODA–POM nanocapsule interaction. Look at the POM nanocapsule / DODA / Octane simulation results from the previous section. How are the DODA molecules oriented around the capsule? How would you describe the properties of the ammonium group at the head of the DODA compared to the carbon tails of the molecule?

2. Now let's look at a lipid molecule. In our work, we will be using a coarse-grain version of the lipid POPC.
   ```
   mol new Structures/POPC.psf
   mol addfile Structures/POPC.pdb
   ```
   How is this molecule organized? How do you think it will interact with the POM nanocapsule–DODA aggregate?

3. In this section, we will be developing a protocol to pack lipids around the DODA-nanocapsule aggregate. We want to know whether a liposomal-like structure will form spontaneously, and if it does, what concentrations of DODA and lipid are required to do this, and at what range of salt concentrations.

4.2 Creating the simulation systems

For these simulations, we will be creating simulation systems much like we did before — except now we want to add lipids, and use water instead of octane.

1. First we want to make a distribution of DODA like we did before. Change directories to `4.Liposome/`. Copy the old `make_DODA_box.tcl` script from the `3.DODA` here. For this simulation, we will have a larger system. Change the box length to 150; change the number of DODA to 168 (reflecting a 76 mM concentration).

2. Run the script and make sure the output was good.

3. Now make the same script for the POPC. Set the box length to 170. We want about 2.2 POPC per DODA ratio. Don't forget to change the `outPrefix`, `segname` and the `topology` file!

4. Run the script and make sure the output was good.

5. Now we will make the entire system. Open up the given script
   `emacs make_full_system.tcl`
   In this script we add all the components together, but then we add water and ions. We add just enough ions to neutralize the system. Make sure that `dodaPrefix` and `popcPrefix` are named the same as those you just made.

6. Run the script and view the results in VMD. Now we're ready to simulate the system.

4.3 Simulating the System

Let's simulate the system we just made. We can use almost the same protocols we used the last time.

1. Copy the NAMD config file you used in `3.DODA`.

2. Edit the NAMD script. The NAMD config won't be that different — all you need to change are the name, the system size (we'll make it a bit bigger than the simulation system, 180 Å in each direction). For these simulations, we'll add in long-range electrostatics (because these drive our aggregation process). Add the following lines to the config file

   ```
   PME Yes
   PMEGridSpacing 3.0
   PMEGridSizeX 128
   PMEGridSizeY 128
   PMEGridSizeZ 128
   ```

3. Run the jobs, either on the command line or on a local cluster. If you do not have time to run the simulations, results from a previous simulation are available in `_Good/`.

4.4 Analyzing the Results

Let's take a look at the results.

1. Load the trajectory in VMD. Don't forget to load the PSF file. What do you see happening?

2. Let's analyze the liposomal aggregate that formed. Make an analysis directory:
   `mkdir Analysis`
   Copy the `Radial_Distribution.tcl` from `3.DODA/` directory here. Edit the script to calculate the bead densities for the capsule, DODA, POPC (resname "POPC") and water (resname "TIP3").

3. Run the analysis and view it in `xmgrace`.

In an actual research project, we would have run many simulations, exploring the regions of DODA concentration and salt concentration for which liposomal aggregates were formed. For this tutorial, we will take the capsule we have, and move on to our next area of research.

5 Fusion of the Liposome with a Membrane

Now that we've shown that liposomal structures readily form when POM nanocapsule are mixed with DODA and POPC, we can test to see if these structures would work as a delivery mechanism to place the POM nanocapsule in a lipid bilayer membrane.

5.1 Modeling the Bilayer

First we need to make a model of the bilayer. We will use VMD's built-in modeling tools to do this.

1. Change directories in VMD and on the command line so that you are working in `5.MembraneFusion`.

2. First we will begin by making an all-atom lipid bilayer membrane using the `membrane builder` plugin in VMD. Open the script `generate_membrane.tcl`. This script, as its name says, generates the all-atom membrane.

3. Load the membrane in VMD.

4. Now we need to take the all-atom membrane and create a coarse-grained model of the bilayer. In VMD, click on the Extensions → Modeling → CG Builder. This plugin creates coarse-grain models when given an all-atom model.

5. Click on "Create a RBCG Model" (Residue-Based Coarse-Grained Model). In the Molecule menu, select the membrane. We want to add a user-defined "CG Database" for our lipids. Click Add, and select `lipid.cgc`. This file defines how to turn all-atom lipids into coarse-grained lipids. Now, click Build Coarse Grain Model

6. Examine the coarse-grained membrane. How does it compare to the all-atom membrane?

5.2 The Simulation System

Now that we have a model for the lipid bilayer membrane we hope to host our POM nanocapsule, we want to simulate the fusion of the POM nanocapsule liposomal structure that we made in the previous section. However, liposome–membrane fusion is a difficult process to simulate. Liposome–membrane and liposome–liposome fusion is a stochastic process which requires the removal of solvation groups around the lipid headgroups at the point of fusion. For our simulation here, we will seed the interaction by connecting a few lipids in the liposome with the bilayer. For more information on the liposome–membrane fusion process, the paper published as a result of this study [1] has more details, including a discussion of published work on simulating membrane fusion.

For this section, we have provided one of the simulation systems from our published work.

1. Open the simulation system, `CapsidMembraneSystem.p*`

2. This is a complicated system, so to get a good visual understanding of the system, it is good to have clean representations. Create the representations in Table 2. For all the representations, use the `Licorice` Coloring Method and the `EdgeShiny` Material. Use a Bond Radius of `2.0` and make sure the Sphere/Bond Resolution is at least `25`.

Selection Text	ColorID
resname CAPS	30
resname DODA and y < 0	8
resname POPC and same residue as name CHO and z > 0 and y < 0	23
resname POPC and same residue as name CHO and z < 0 and y < 0	21

3. Examine the system. Where has the liposome–membrane interaction been seeded? You can create water and ion selections to see the solvation box we will use.

5.3 Simulating the Fusion Process

Now let's take a look at the simulation process. For these simulations, we have provided DCDs without water or ions — this helps keep the simulation size down.

1. Open the simulation files, `CapsidMembraneNoWater.psf`, and the first DCD file `CapsidMembrane_Fusion1.dcd`.

2. Go back to the first frame of the simulation, and copy the representations you made into the new molecule with the Clone Representations plugin: Extensions → Visualization → Clone Representations. (Make sure you are on the first frame when you do this, so that the `z >< 0` expressions work. You can also change to the first frame, then hit the Apply button in the Graphical Representations toolbox.)

3. Now examine the trajectory. What is happening to the bilayer? To get a better look, try chopping the bilayer down in the x-z plane by viewing only the lipids that are `y > 0`. The effect we are seeing here, the drastic bowing of the bilayer, is aphysical and due to the periodic nature of MD simulations — the MD simulation is periodic in the plane of the membrane, so the bending modes of the membrane are determined by the size of the system. Unfortunately, the number of atoms in the system scales like $\text{Area}^2_{\text{bilayer}}$, so for practical purposes, we need to simulate a small and finite system.

4. To overcome this, we will decrease the tension by flipping lipids at the edge of the system from the top leaflet of the bilayer to the bottom. This mimics the reduction in strain that we would see in a real-life bilayer. To view this process, load the next step in the simulation, `CapsidMembrane_Fusion2.dcd`.

5. What happens in this simulation? Why do you think the POM nanocapsule is stable in the bilayer? In this state, could it be used as a synthetic ion channel?

6. To answer this question, we performed simulations with the lipids above and below the capsule removed — sort of a "what if" situation. You can view the results of these simulations in `CapsidMembrane_Open.psf/dcd`.

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