Sampling Protein-Lipid Interactions with Swarms of Trajectories and a Transition Matrix Analysis

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Introduction

- Determining membrane protein lipid solvation is experimentally challenging
- Using long simulations to predict first shell lipids is costly, with uncertain convergence
- We return to an algorithm we introduced recently [1], Coarse Grained Transition Matrixes with swarms of short swarm, trajectories run in parallel
- Systematically checked coarse grained molecular dynamics simulations of various lengths and initial compositions demonstrates a shortcomings with this method

Methods

- Protein used is $A_{2A}R$ GPCR in inactive state
- Ternary systems are composed of DPPC:DOPC:CHOL (55:15:30)
- Coarse-grained Molecular Dynamics simulation preformed with MARTINI force field 2.2 [2] and GROMACS[1] 2018
- 4 simulation types
  - 3 15μs simulations (**Long Simulation)**
  - 50 50ns simulations for 1 initial state (**Short Single State**)
  - 50 50ns simulations from random initial states (**Short Multi-State**)
  - 90 50ns simulations from quasi-random initial states (**Short Expanded-States**)
- Voronoi Tessellation [5] to predict first shell counts (Fig1.)
- Construct coarse grained transition matrix [1]

Definitions

- π^{eq} is the equilibrium distribution from the coarse grained transition matrix
- π is the naive probability obtained from a simple average of sampled states
- $\Delta\pi$ the difference between π and π^{eq}
- $\psi(t) = \frac{1}{3}\sum_{l}\frac{x_l(t)}{x_{l,i}}$; Compares weighted average composition at time t to the initial state composition
  - $\psi(t)$=1 the same, $\psi(t)$> or < 1 diverges

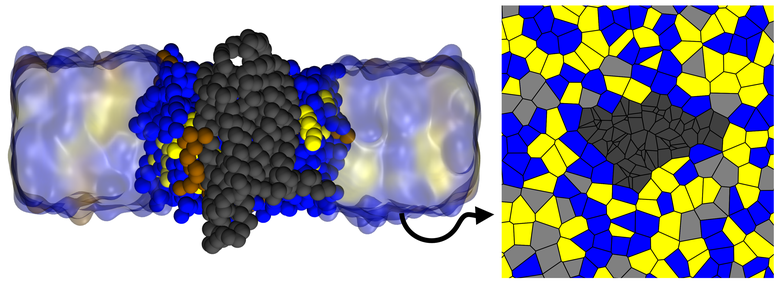

Fig 1. Example MD and Voronoi Tessellation [5]. Each color is a lipid species, each polygon represents a lipid. First shell lipids are defined as lipid in direct contract with the protein (shown as beads). Protein is shown in dark grey. Membrane is ~17x17 nm.

Unique states are not observed in simulations starting from a single or multiple initial compositions

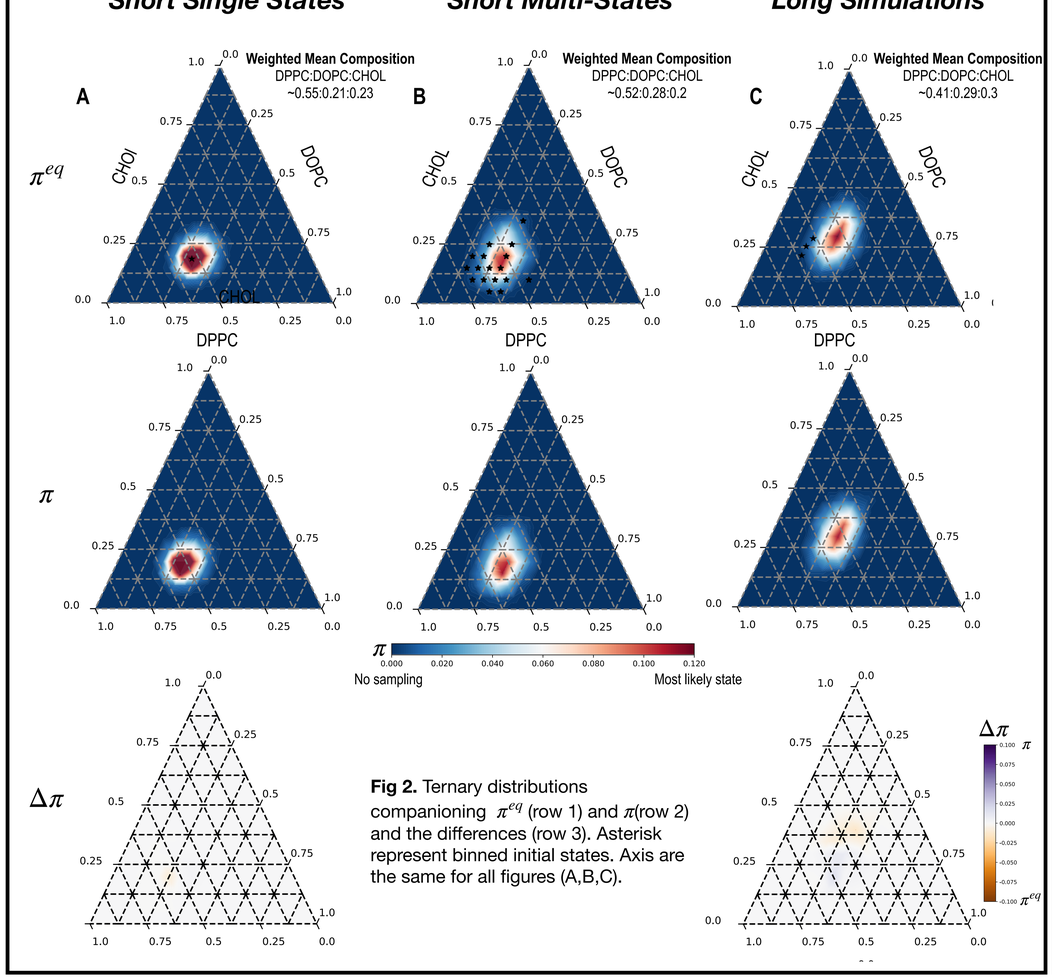

Fig 2. Ternary distributions companioning π^{eq} (row 1) and π(row 2) and the differences (row 3). Asterisk represent binned initial states. Axis are the same for all figures (A,B,C).

Short simulations require substantial initial states to sample key states in long simulations

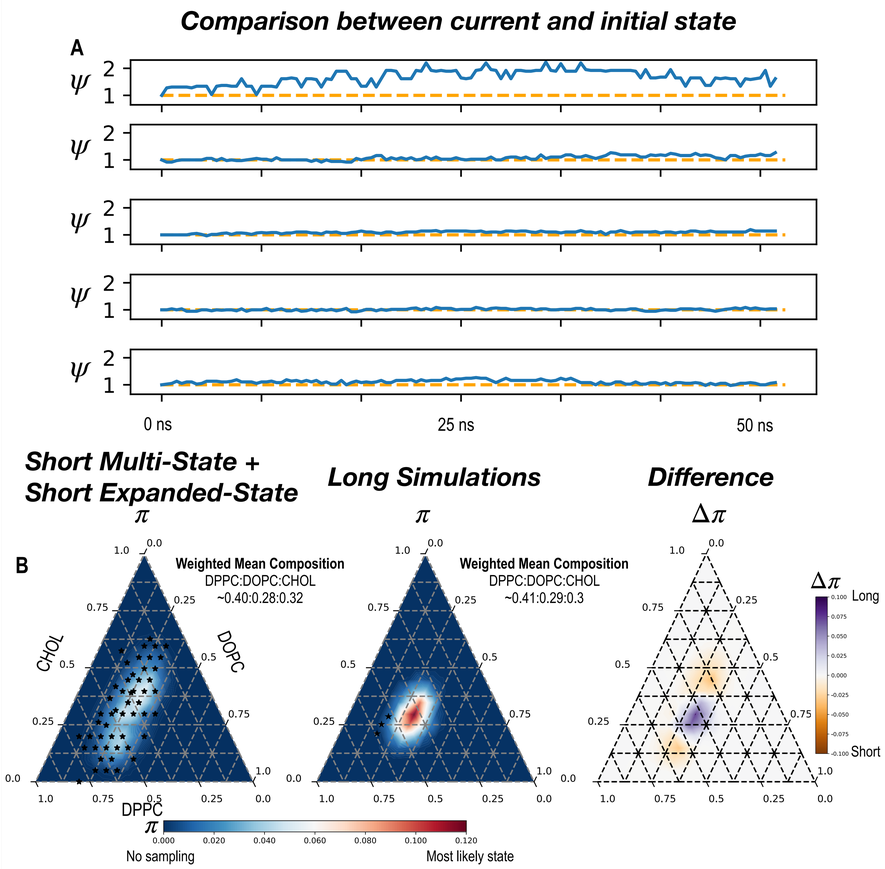

Fig 3. A. Comparing first shell composition at time t to initial state over the course of 5 different short trajectories. Orange lines show if the ratios are identical, blue are the actual ratios. **B**. Adding **Short Multi and Expended-State simulations** improves overlap with **long** simulation. Asterisk represent binned initial states. Axis are the same for all figures.

Summary

- Rare states not observed using CGTM and short swarm simulations
- Much of state space must be sampled for short simulations to overlap large simulations
- **What is the potential problem:**
  - Initial states over populate the CGTM
  - Short simulations are "stuck" at locations near initial states and long simulations after equilibrium
- **Potential Fixes:**
  - Reweighting algorithm [2]
  - Specific initial state choices based on long simulations
  - Introduce spacial coordinates into the CGTM
  - Only sample form simulations like **Fig 3A top**

Citations

1. Leonard, Lyman, Biophys. J. (2021), https://doi.org/10.1016/j.bpj.2021.02.029, **2.** Russo, Zuckerman, et al., pre-print (2021), arXiv:2105.13402, **3.** Berendsen, et al., Comp. Phys. Comm (1995), https://doi.org/10.1016/0010-4655(95)00042-E, **4.** D.H. de Jong, et al. J. Chem. Th. Comp, 2013,. DOI:10.1021/ct300646g. **5.** Alexander Sodt, Voronoi Tessellation https://github.com/alexsodt/voronoi

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