Supporting Information

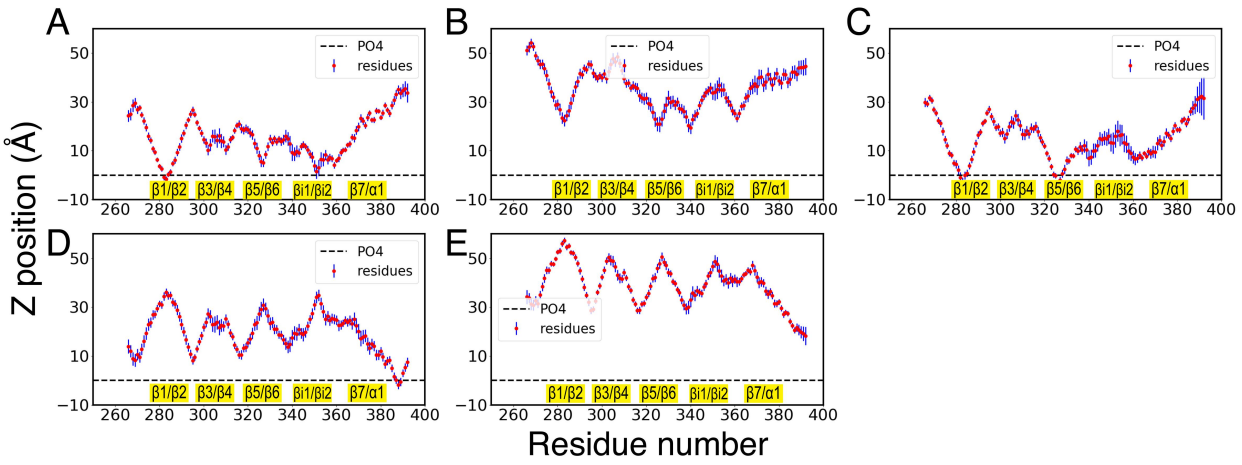

Figure S1: Ensemble-averaged Cα profile of GRP1-PHD calculated during last 50 ns of HMMM simulations in the presence of pure PC lipid bilayers. In two of the five independent membrane-binding simulations (A and C), GRP1-PHD associated with the lipid bilayer, however, in other replicas (B, D and E), it remains unbound.

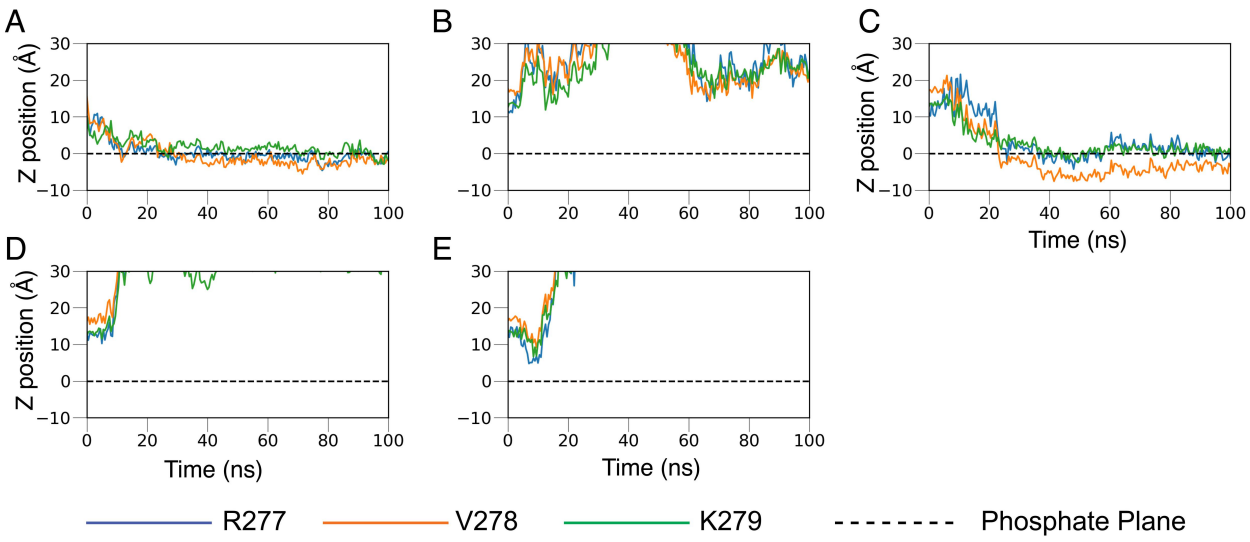

Figure S2: Time evolution of the height of the side chain COM of R277, V278, and K279 with respect to the phosphate plane (dashed line) in pure PC membrane binding HMMM simulations. A negative coordinate of COM indicates that the residue lies below the phosphate plane and therefore are closely engaged with the membrane.

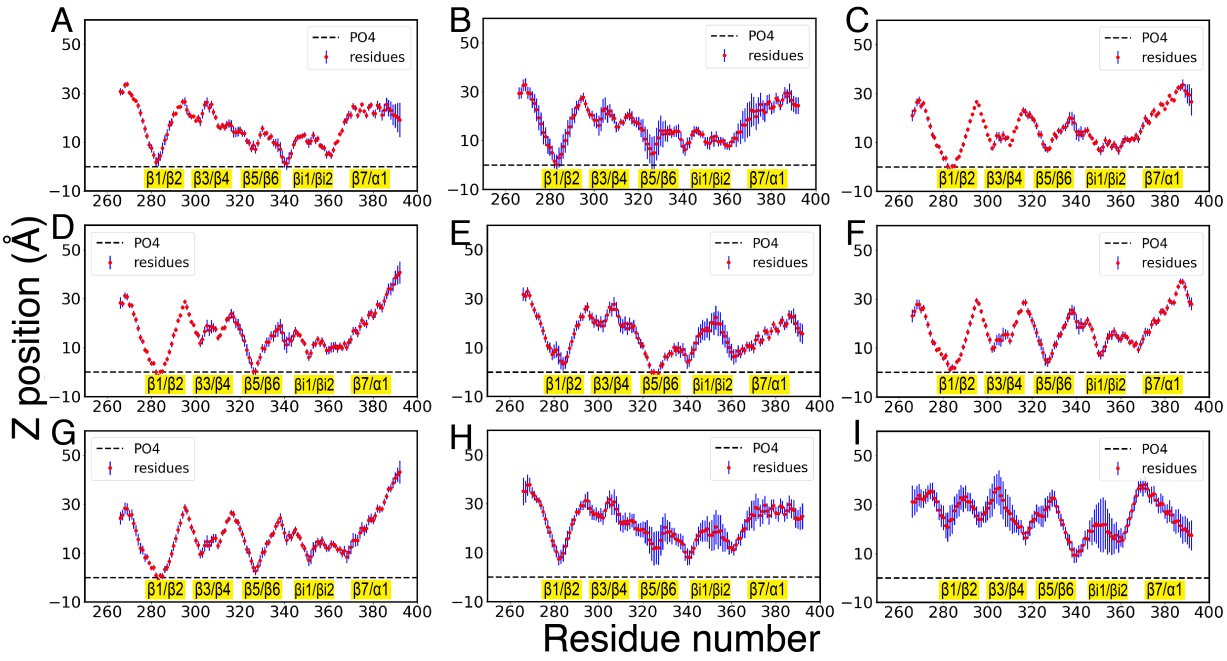

Figure S3: Ensemble-averaged Cα profiles of the GRP1-PHD in PC:PS bilayer (80:20), calculated during last 50 ns of HMMM membrane binding simulations. In seven of the simulated replicas, GRP1-PHD associated itself to the lipid bilayer, however, in two of the replicas (E and I) GRP1-PHD remained unbound. The blue bars denote the standard deviation in the residue distances. All the membrane interacting loops are highlighted in yellow.

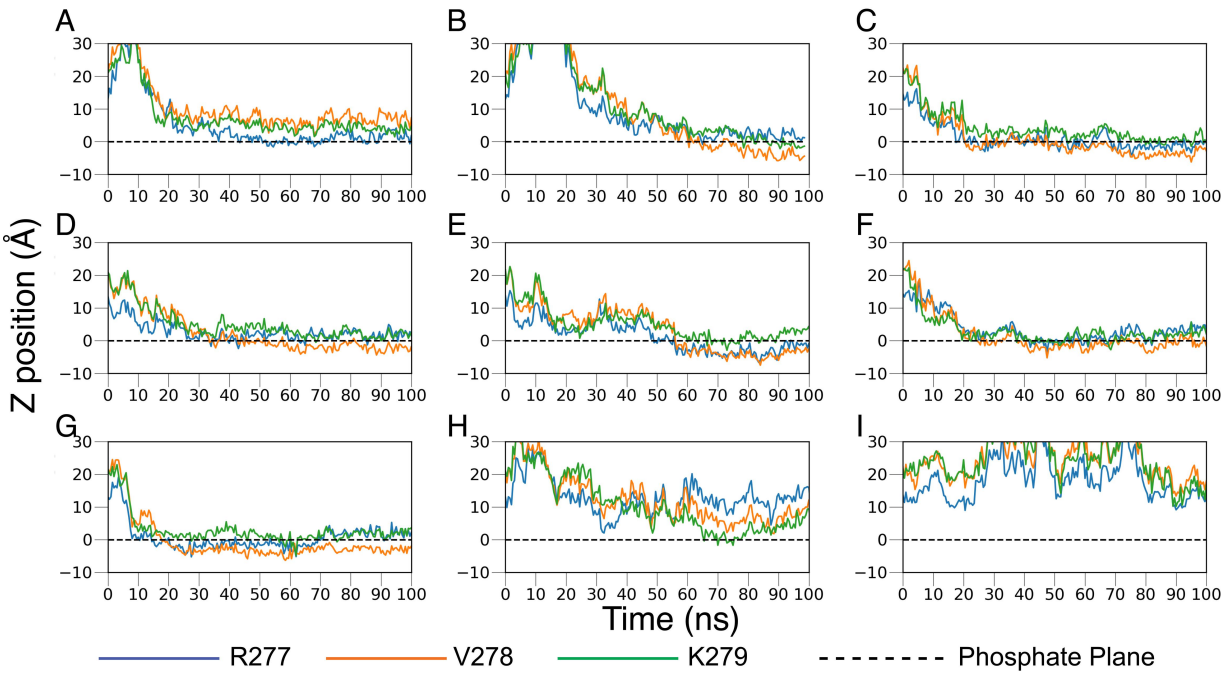

Figure S4: Time evolution of side-chain COM of R277, V278, and K279 in PC:PS bilayer (80:20), captured from HMMM simulations. The negative coordinate of COM indicates that those residues lie below the phosphate plane and are therefore closely engaged with the membrane. In all the replicas, except replicas H and I, GRP1-PHD binds the membrane within 100 ns. In replica H, after the an initial collision with the membrane GRP1-PHD moves away from lipid bilayer, while in replica I, it never comes in contact with the lipid bilayer.

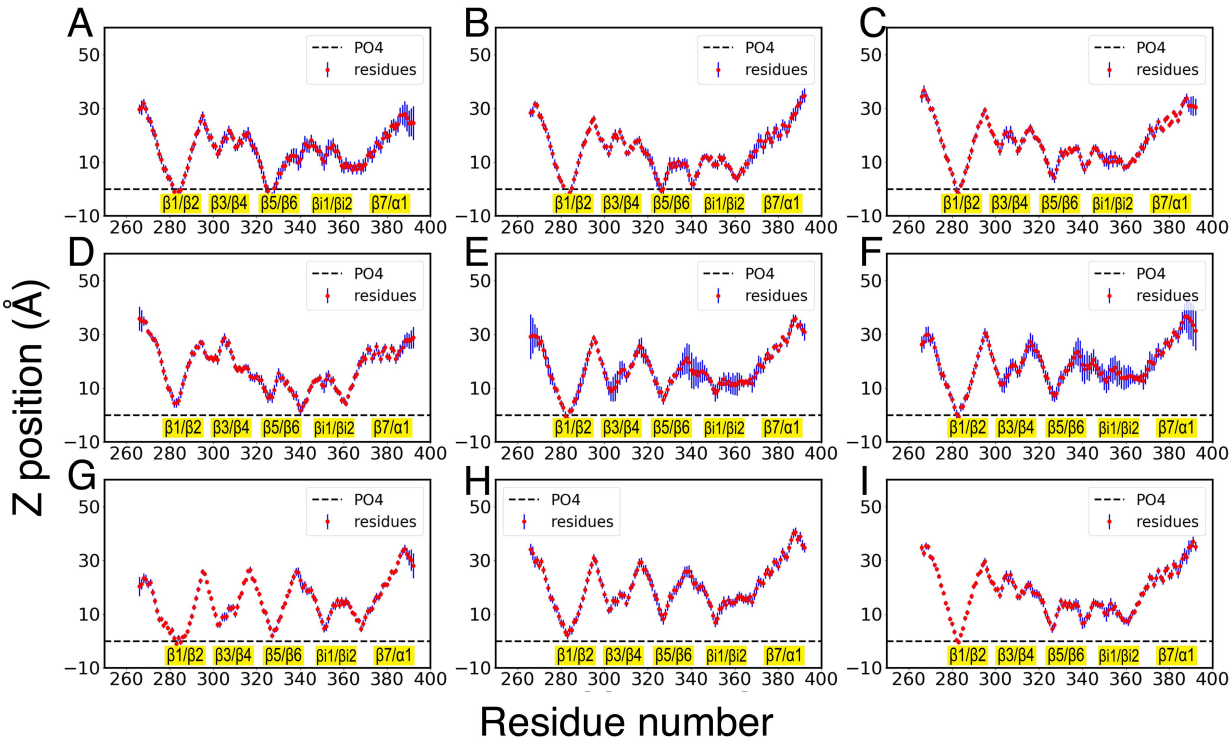

Figure S5: Ensemble-averaged Cα profiles of the GRP1-PHD in PC:PS:PIP_3 bilayer (80:19:1), calculated during last 50 ns of 9 independent HMMM membrane binding simulations. When PIP_3 is present, in all replicas GRP1-PHD binds the membrane.

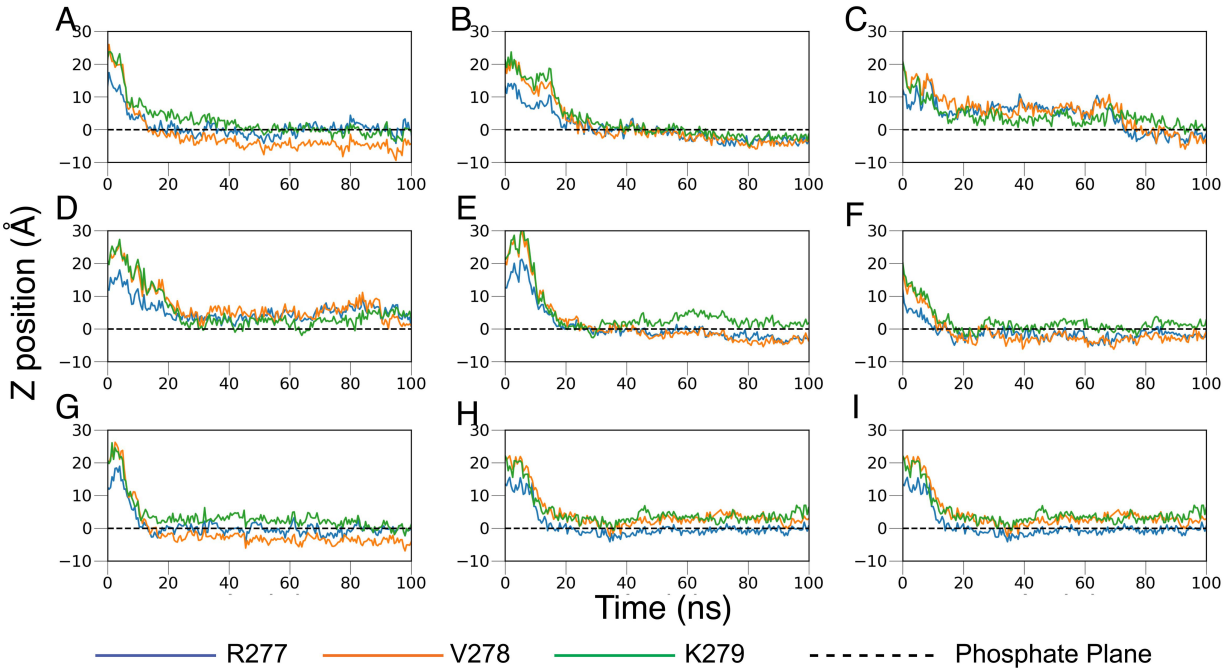

Figure S6: Time evolution of side chain COM of R277, V278, and K279 in PC:PS:PIP_3 bilayer (80:19:1), plotted for 9 independent HMMM simulations. A negative coordinate of COM indicates that those residues lie below the phosphate plane and are therefore closely engaged with the membrane. At the end of the MD simulations in all the replicas (A-I), GRP1-PHD binds the membrane.

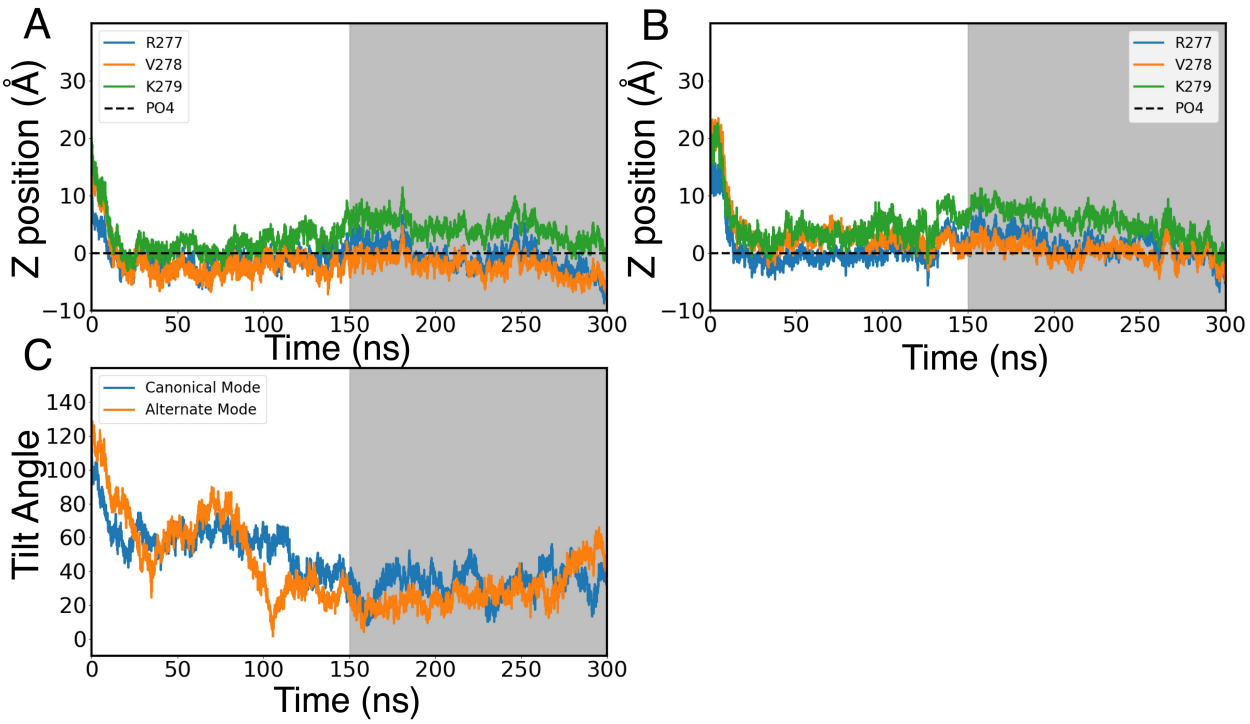

Figure S7: Time evolution of side-chain COM of R277, V278, and K279 in: (A) C and (B) A binding modes. Throughout the HMMM and full membrane (shown on a grey background) simulations, GRP1-PHD remains bound to the PIP_3 lipid.(C) The tilt angle of GRP1-PHD in the two binding modes remains stable upon conversion to full membranes.

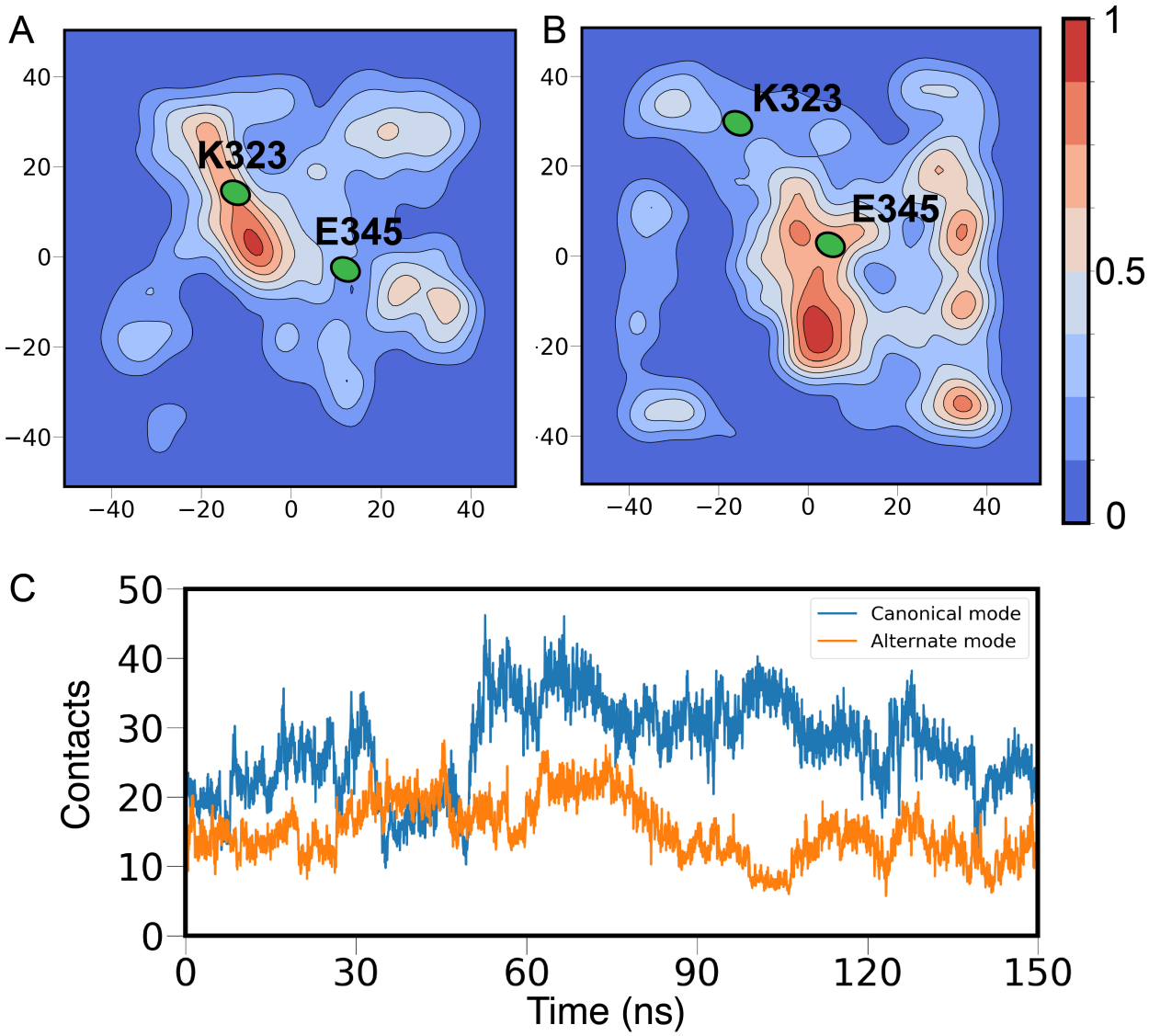

Figure S8: The occupancy map of PS lipids in: (A) C and (B) A binding modes. The occupancy maps are calculated using 140 ns of the simulation in full membrane. The GRP1-PHD is shown with green contour lines. Green dots signifies the protein residues. (C) Time series of the number of contacts formed between GRP1-PHD and the PS lipids. A distance cutoff of 3.5 Å was used in the contact analysis.

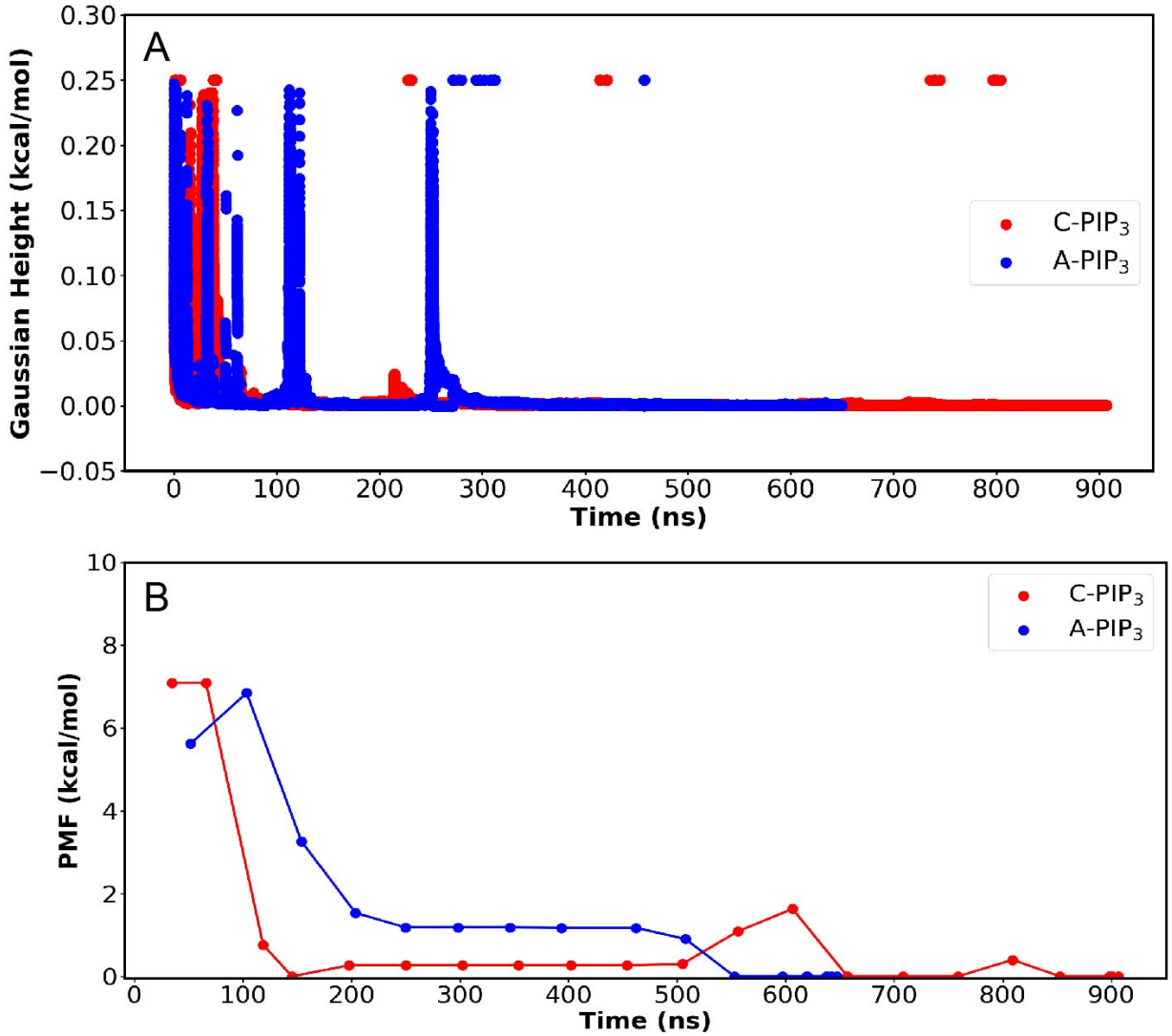

Figure S9: Convergence check for WT-MetaD simulations. (A) The time evolution of the bias or the Gaussian hill height which nears 0. It remains nearly invariable in the last 100-150 ns of the simulation. (B) The time evolution of the free energy minima at 20 Å and 25 Å for C and A binding modes, respectively, plotted at 50 ns intervals.

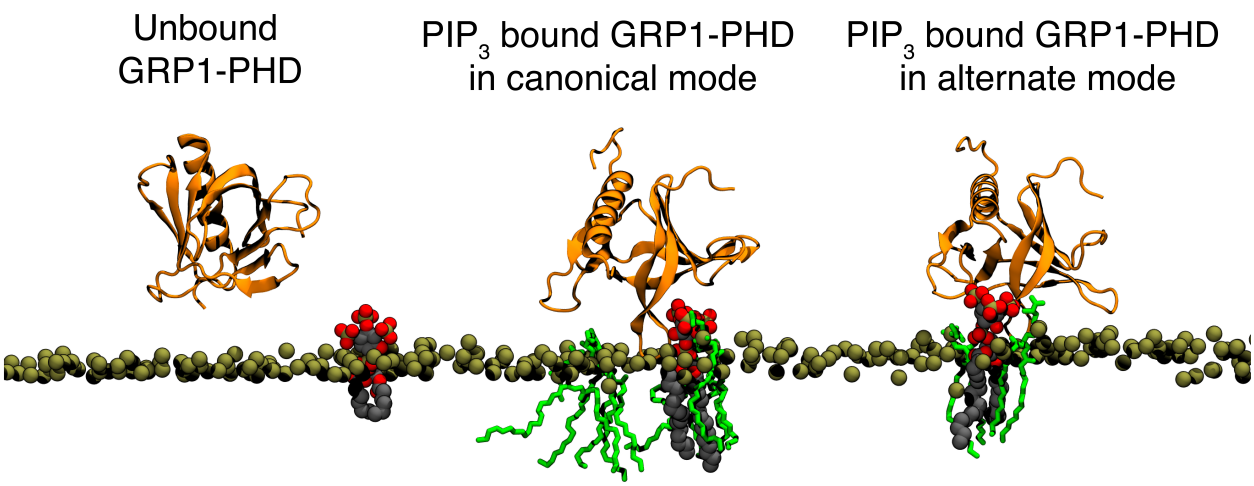

Figure S10: TOC

Table S1: Summary of GRP1-PHD residues average binding depth

Side Chains	**PC:PS**	**PC:PS:PIP$_3$**
R277	1.2±2.7	-1.5±1.0
V278	-2.8±2.0	-1.7±2.6
K279	1.8±2.0	1.5±2.2

Table S2: Hydrogen bonding residues in canonical PIP$_3$ binding mode (C-mode)

Donor	**Acceptor**	**Occupancy %**
R277	PIP$_3$	47.8
K282	PIP$_3$	94.9
Y298	PIP$_3$	39.2
R284	PIP$_3$	100.0
K273	PIP$_3$	42.3

Table S3: Hydrogen bonding residues in alternate PIP$_3$ binding mode (A-mode)

Donor	**Acceptor**	**Occupancy %**
R283	PIP$_3$	100.0
R322	PIP$_3$	88.2
K323	PIP$_3$	100.0