



All-atom models of HIV-1 Env spike

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Outline

1. Ectodomain models based on Tri-FPPR Class 6
2. Membrane-anchored SOSIP-MPER-TM models
3. Conclusions
4. Upcoming

Ectodomain models based on Tri-FPPR Class 6

Models derived from class-6 Tri-FPPR cryo-EM structure

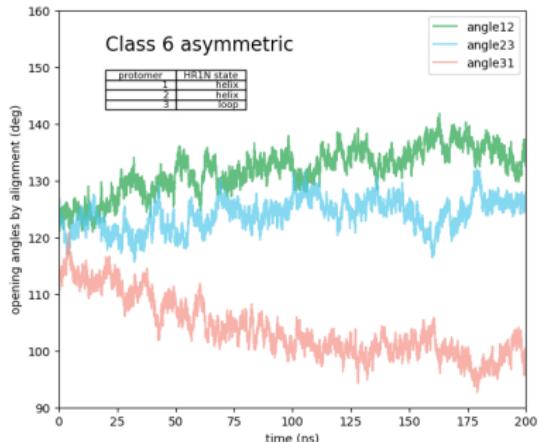
name	Protomers with		
	HR1N unfolded	MPER	notes
C6-FT-HHL*	3	1	as-received class-6 structure
C6-FT-LHL	1,3	1	
C6-FT-LLL	1,2,3	1	
C6-S1-HHH	–	1,2,3	C_α -aln-replication of protomer 1
C6-S1-LLL	1,2,3	1,2,3	(1) C_α -aln-replication of protomer
C6-S1-LLLb	1,2,3	1,2,3	(2) C_α -aln-replication of protomer
C6-S1-LLLc	1,2,3	1,2,3	C3-replication of protomer 1

MD Simulation General Details

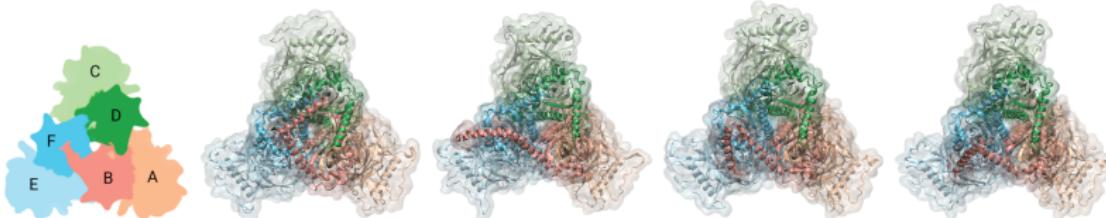
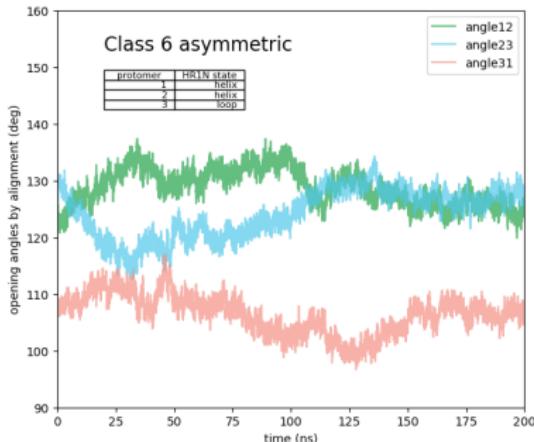
- All-atom models with all glycan stems retained
- All systems built using pestifer
- Solvated in explicit water (TIP3P)
- System sizes 320,000 to 340,000 atoms
- NAMD v 2.14 using CHARMM-FF v36
- Production MD: NPT (310 K, 1 bar) for 200 ns (100,000,000 time-steps)
- Observables:
 - opening angles measured via protomer alignment (on gp120 and gp41 separately)
 - HR1N alpha helicity (not shown in this talk)
 - snapshots

C6-FT-HHL (as-received Tri-FPPR class 6 cryo-EM model)

gp120 alignment



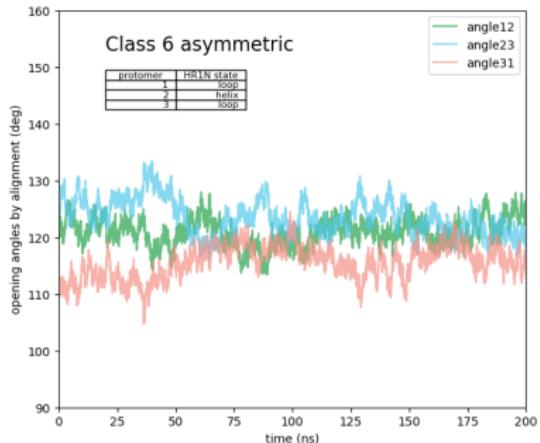
gp41 alignment



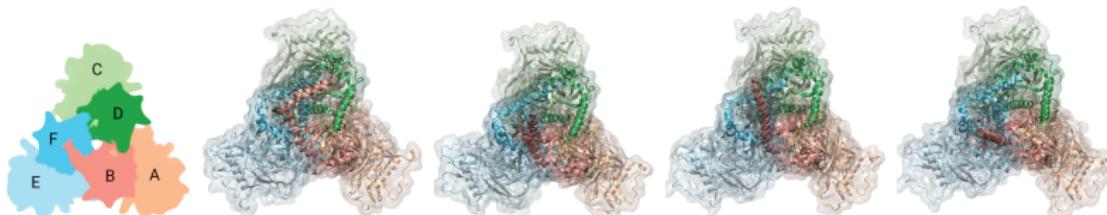
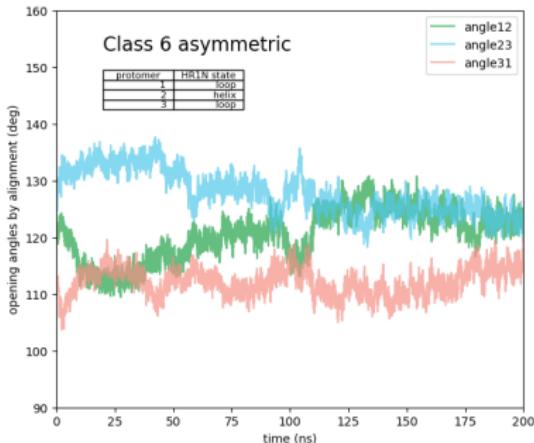
Protomer 1 MPER “flops out” and binds to protomer 3 gp41

C6-FT-LHL (HR1N unfolded in protomer 1 and 3)

gp120 alignment



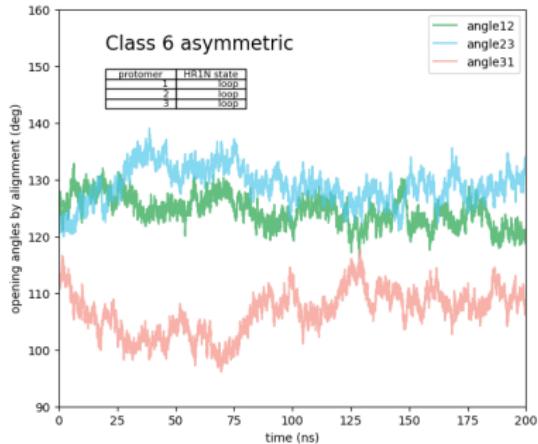
gp41 alignment



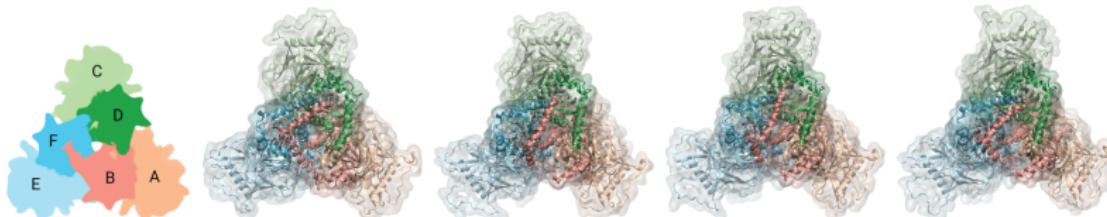
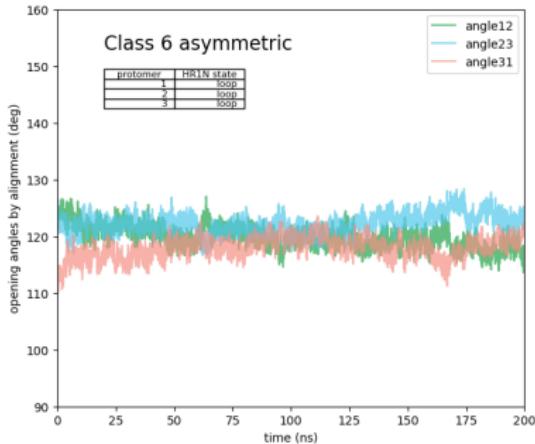
Protomer 1 $\alpha 9$ and MPER become one helix

C6-FT-LLL (HR1N unfolded in all protomers)

gp120 alignment



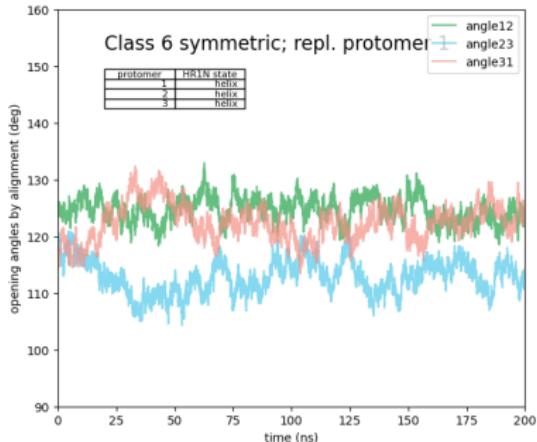
gp41 alignment



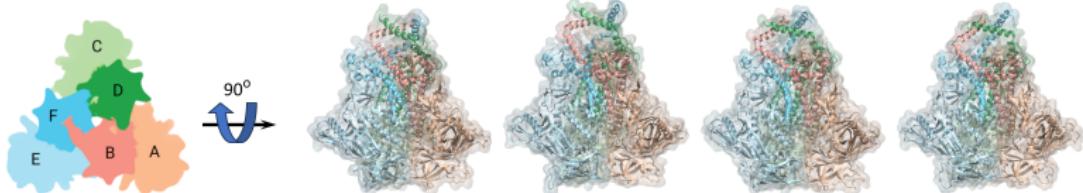
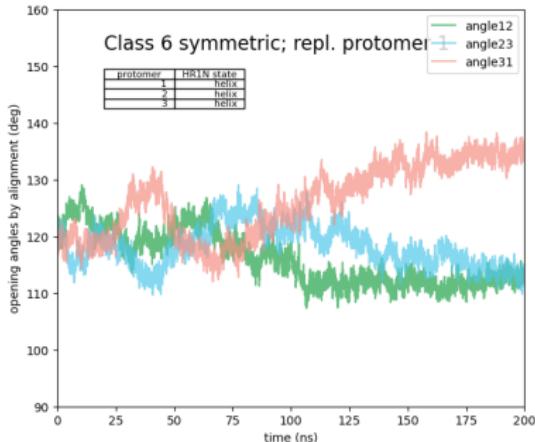
Protomer 1 MPER remains relatively stable

C6-S1-HHH (Protomer 1 replicated onto 2, 3)

gp120 alignment



gp41 alignment

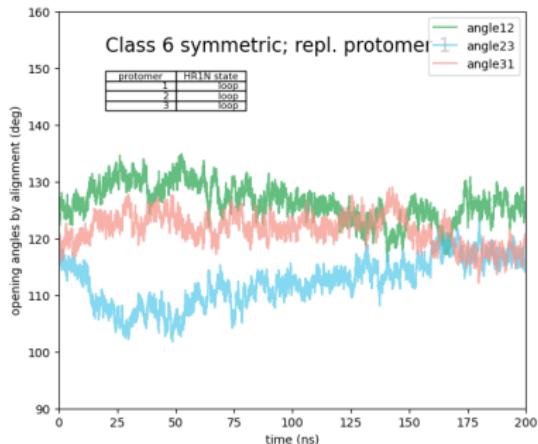


MPERs move a little

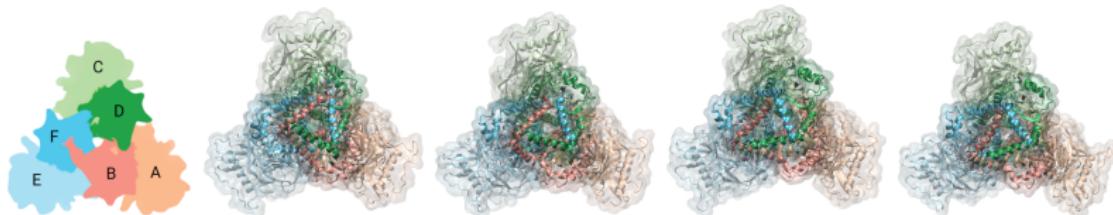
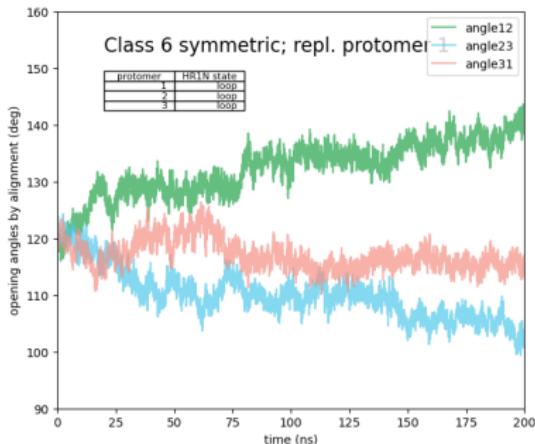
C6-S1-LLL

(Protomer 1, unfolded HR1N, replicated onto 2, 3)

gp120 alignment



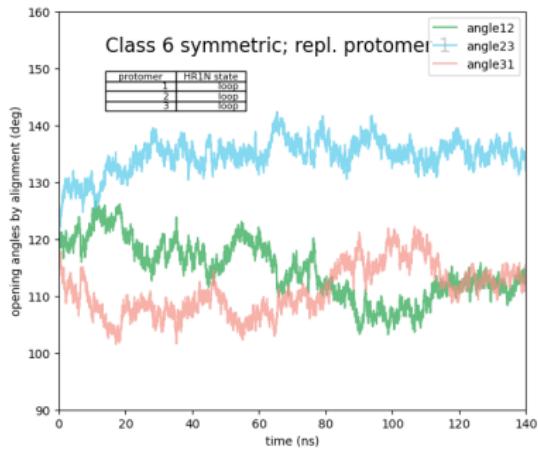
gp41 alignment



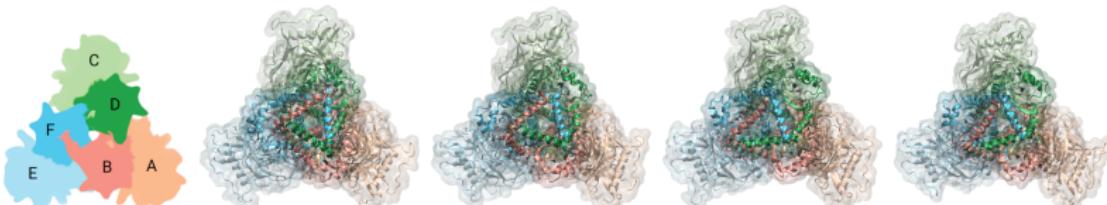
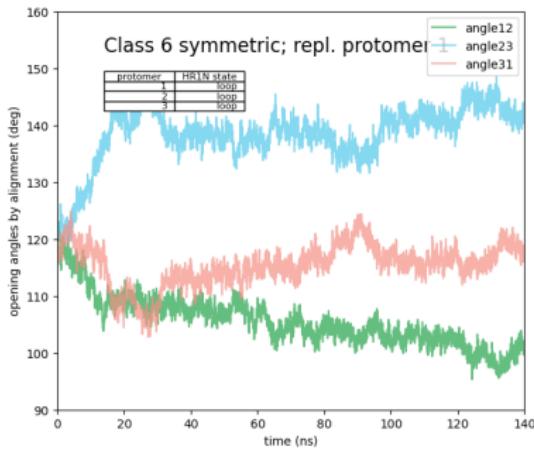
gp41s become asymmetric

C6-S1-LLLb (Protomer 1, unfolded HR1N, replicated onto 2, 3; second replica)

gp120 alignment

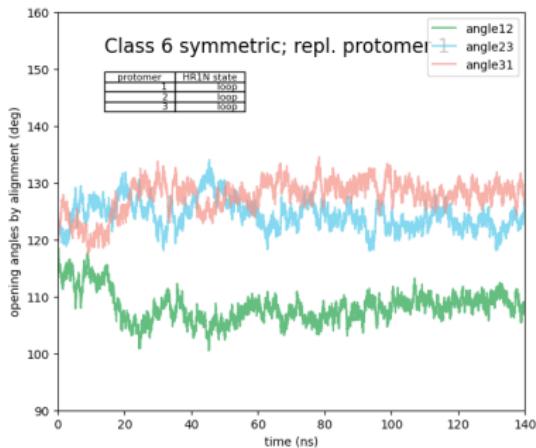


gp41 alignment

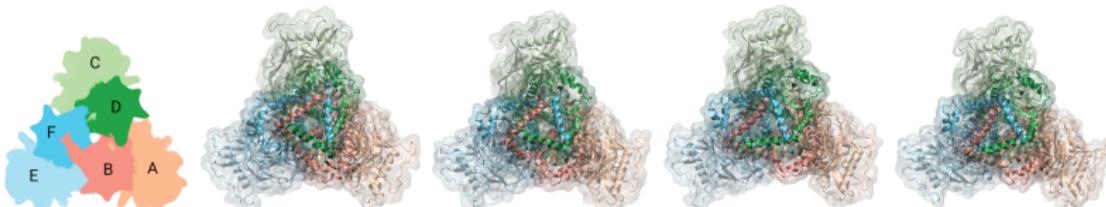
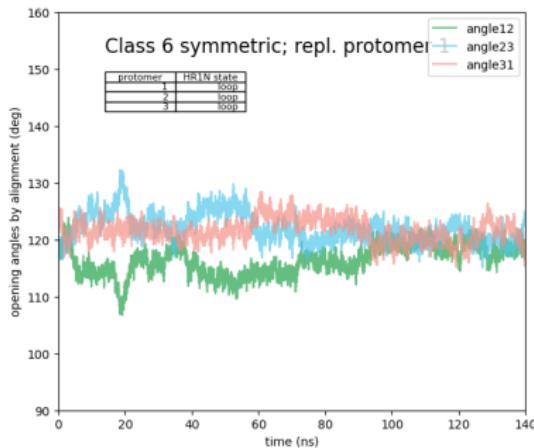


C6-S1-LLLc (Protomer 1, unfolded HR1N, replicated onto 2, 3; third replica)

gp120 alignment



gp41 alignment



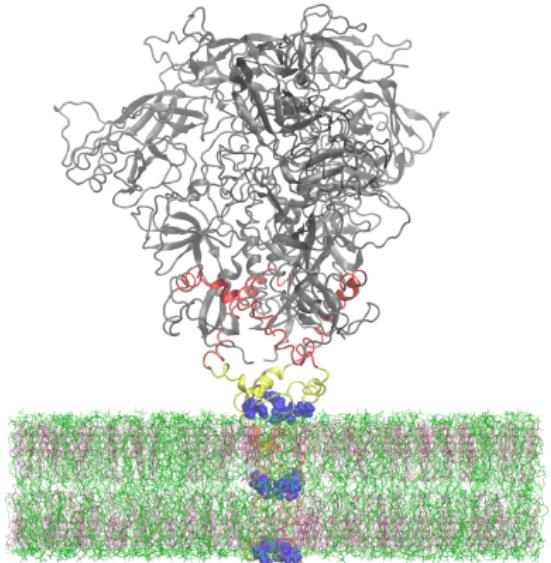
Membrane-anchored SOSIP-MPER-TM models

Models derived from SOSIP Envs and NMR MPER-TM trimers

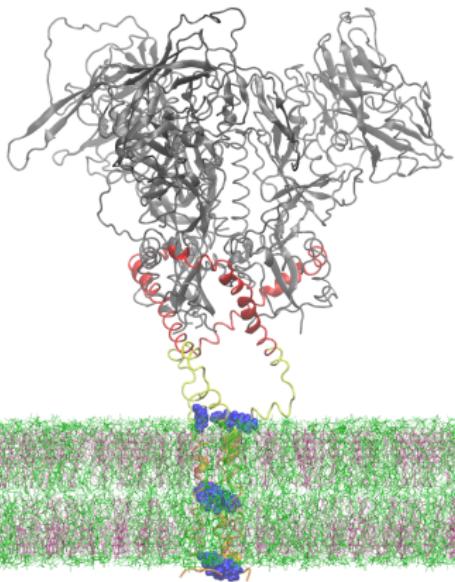
- SOSIPs used are 4zmj (state 2) and 5vn3
- all ligands removed, engineered mutations reverted to WT
- gp41's grown out to 687 and then ligated onto MPER-TM 6e8w
- Relaxed via MD with TM's held in place
- Currently investigating membrane embeddings (z-position of midplane)

Models derived from SOSIP Envs and NMR MPER-TM trimers

4zmj (state 2)



5vn3 (state 3)



α_9 ; MPER; TM-Lys/Arg; TM; DOPC:CHOL (1:1)

Conclusions

Conclusions

- Tri-FPPR model MD Simulations:
 - Single-MPER trimers show poor packing of MPER
 - Asymmetric trimers remain asymmetric
 - Unfolding all HR1N's can reduce trimer asymmetry
- Membrane-anchored SOSIP-MPER-TM models
 - Some ambiguities with membrane embedding need addressing

Upcoming

Upcoming Plans

- Target models:
 - membrane-embedded Tri-FPPR-TM (various configurations of HR1N)
 - membrane-embedded state-3 SOSIP(5vn3)-MPER-TM(6e8w) (all engineered mutations reverted)
 - membrane-embedded state-2 SOSIP(4zmj)-MPER-TM(6e8w) (all engineered mutations reverted)
- Membrane model: 50% POPC, 50% CHOL
- Big questions
 - **How do MPERs pack with interprotomer contacts to both gp120 and gp41?**
 - **How is MPER-TM embedded in membrane in context of ectodomain?**

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