



# All-atom models of HIV-1 Env spike

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March 21, 2024

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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**

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

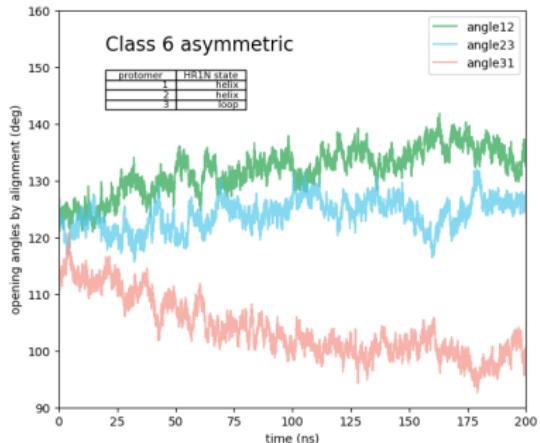
name	Protomers with		
	HR1N unfolded	MPER	notes
C6-FT-HHL*	3	1	as-received class-6 structure
C6-FT-LHL	1,3	1	
C6-FT-LLL	1,2,3	1	
C6-S1-HHH	–	1,2,3	$C_\alpha$ -aln-replication of protomer 1
C6-S1-LLL	1,2,3	1,2,3	(1) $C_\alpha$ -aln-replication of protomer
C6-S1-LLLb	1,2,3	1,2,3	(2) $C_\alpha$ -aln-replication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

## MD Simulation General Details

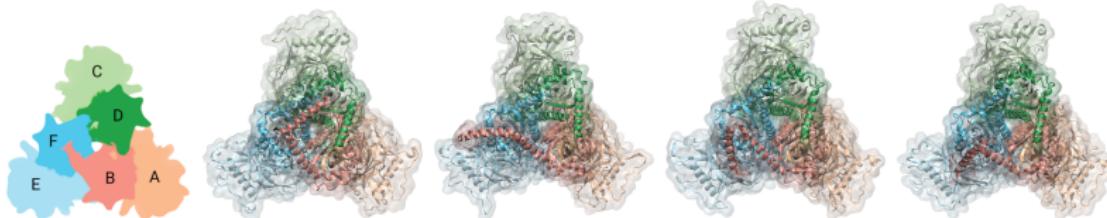
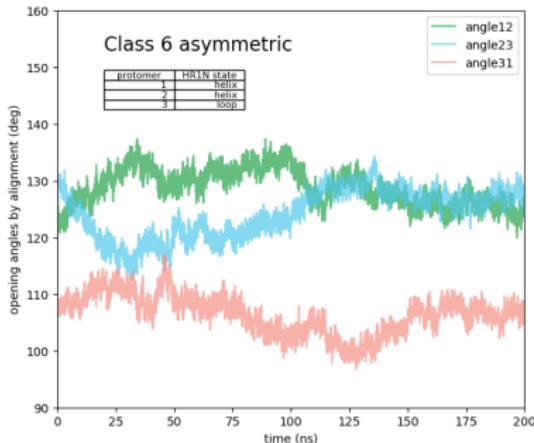
- All-atom models with all glycan stems retained
- All systems built using pestifer
- Solvated in explicit water (TIP3P)
- System sizes 320,000 to 340,000 atoms
- NAMD v 2.14 using CHARMM-FF v36
- Production MD: NPT (310 K, 1 bar) for 200 ns (100,000,000 time-steps)
- Observables:
  - opening angles 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



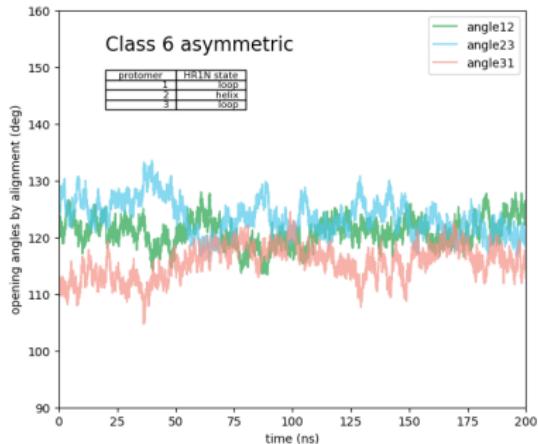
gp41 alignment



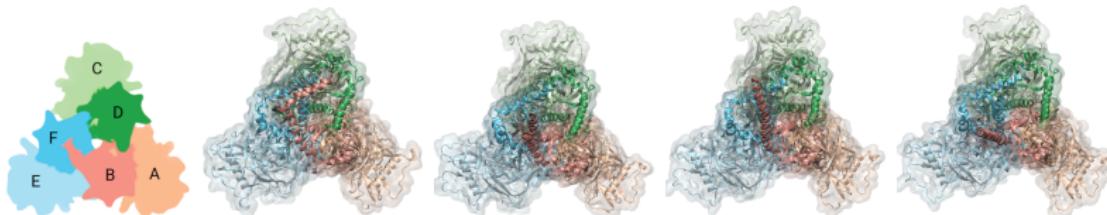
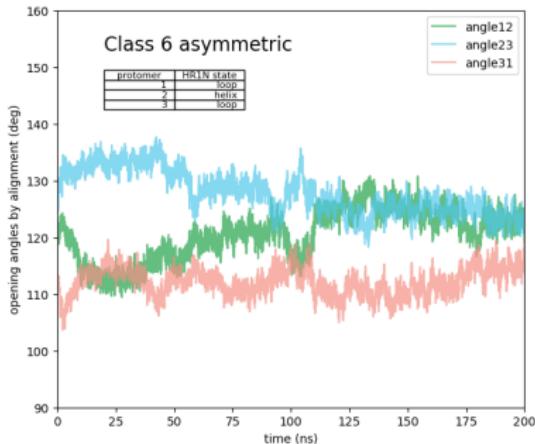
Protomer 1 MPER “flops out” and binds to protomer 3 gp41

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

gp120 alignment



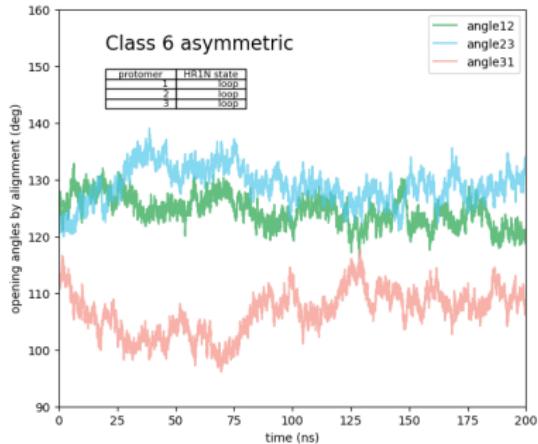
gp41 alignment



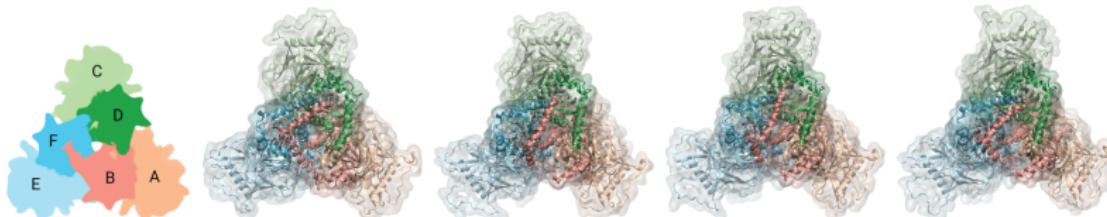
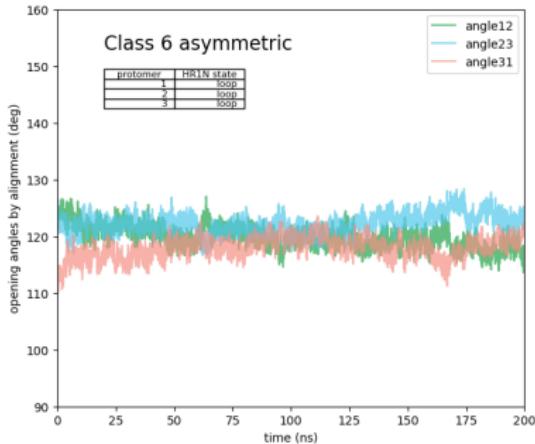
Protomer 1  $\alpha 9$  and MPER become one helix

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

gp120 alignment



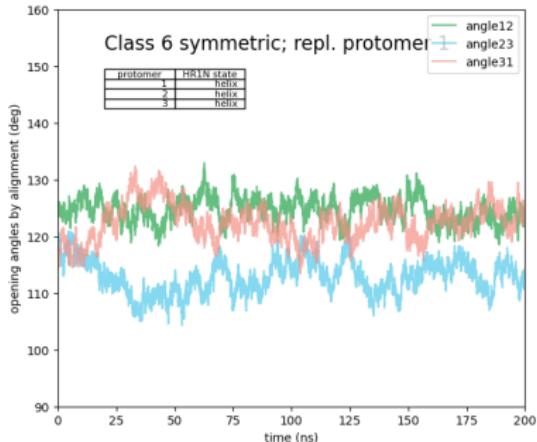
gp41 alignment



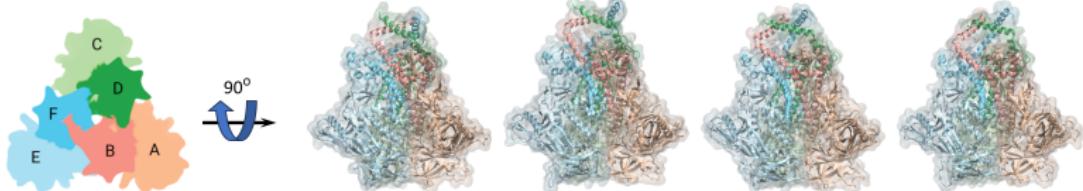
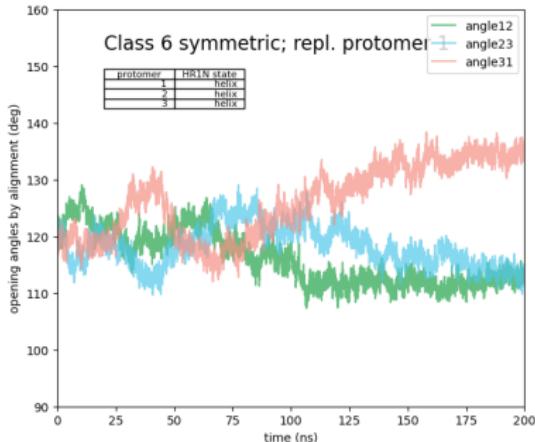
Protomer 1 MPER remains relatively stable

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

gp120 alignment



gp41 alignment

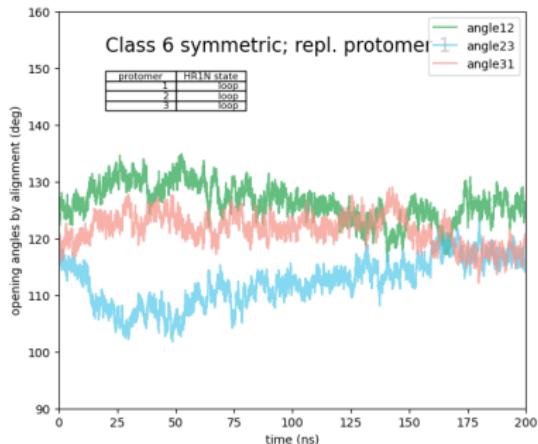


MPERs move a little

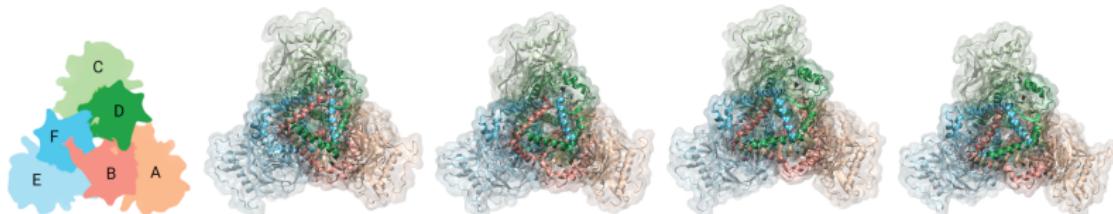
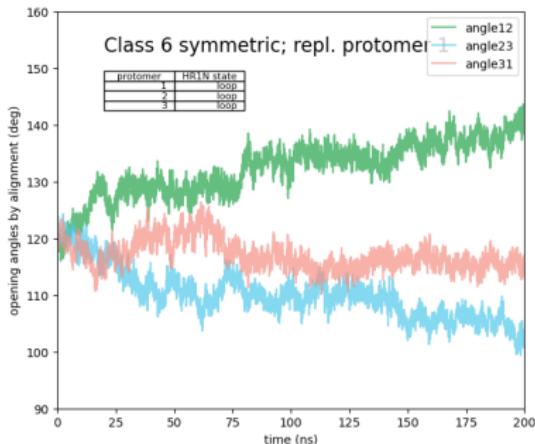
# C6-S1-LLL

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

gp120 alignment



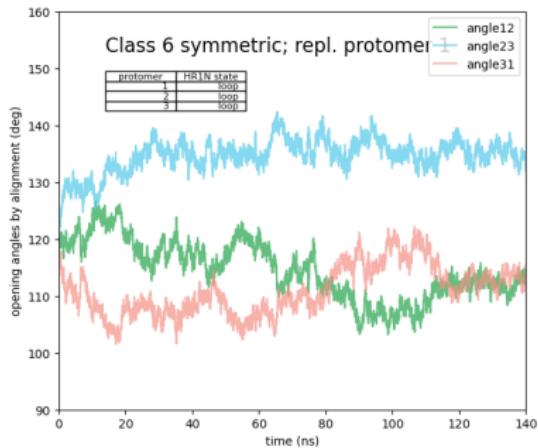
gp41 alignment



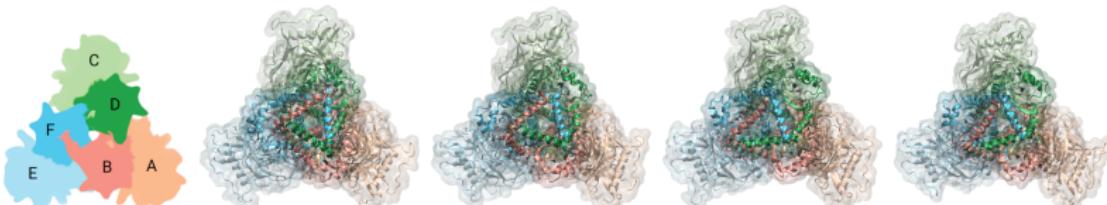
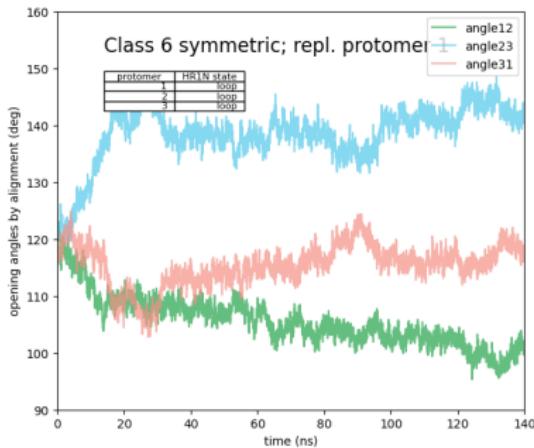
gp41s become asymmetric

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

gp120 alignment

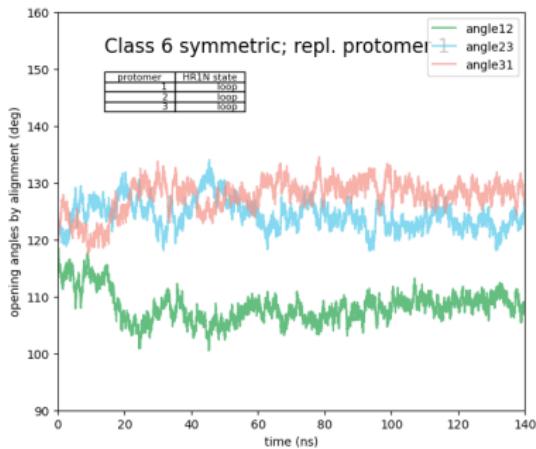


gp41 alignment

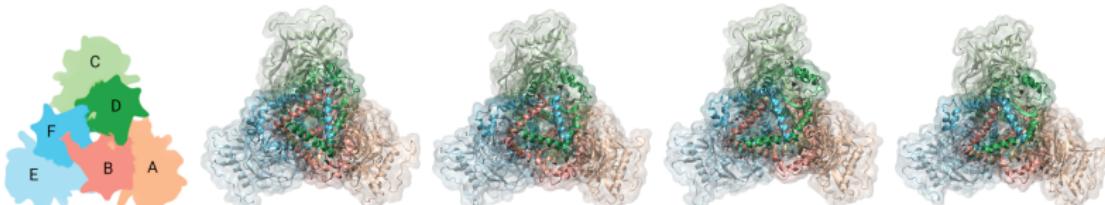
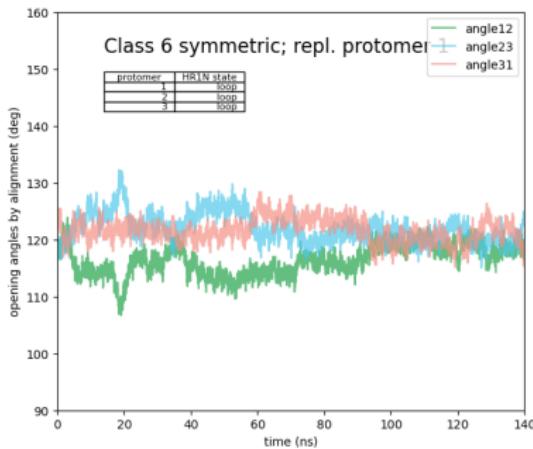


# C6-S1-LLLc (Protomer 1, unfolded HR1N, replicated onto 2, 3; third replica)

gp120 alignment



gp41 alignment



# **Membrane-anchored SOSIP-MPER-TM models**

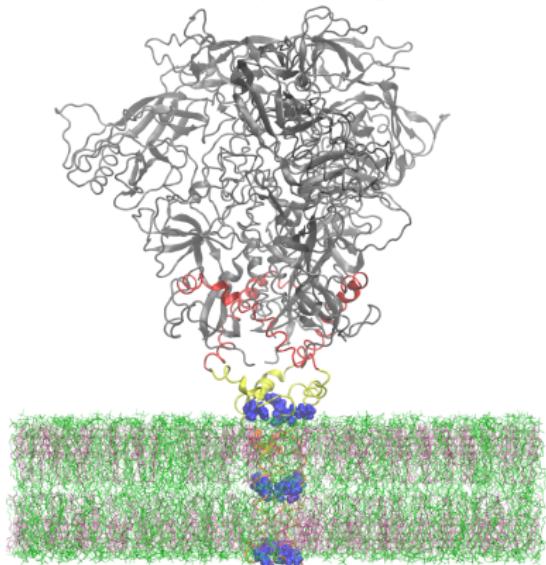
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## Models derived from SOSIP Envs and NMR MPER-TM trimers

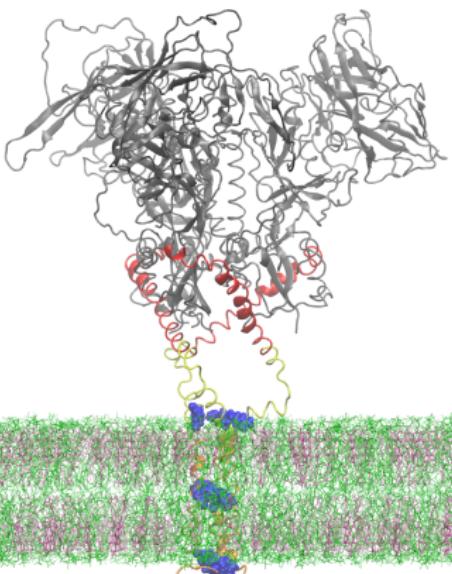
- SOSIPs used are 4zmj (state 2) and 5vn3
- all ligands removed, engineered mutations reverted to WT
- gp41's grown out to 687 and then ligated onto MPER-TM 6e8w
- Relaxed via MD with TM's held in place
- Currently investigating membrane embeddings (z-position of midplane)

# Models derived from SOSIP Envs and NMR MPER-TM trimers

4zmj (state 2)



5vn3 (state 3)



## Conclusions

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# Conclusions

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- 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

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# Upcoming Plans

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- 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?**

# Acknowledgments

## Dana Farber Cancer Institute

Shijian Zhang

Zhiqing Zhang

Saumya Anang

Hanh Nguyen

Joe Sodroski

## Yale University

Ruixue Xu

Walter Mothes

Funding: NIH R01 AI178833