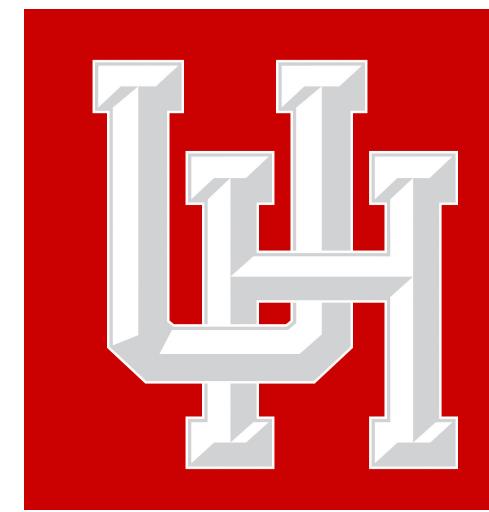


Investigating the Stabilizing Effect of the R14del Mutation on Phospholamban Pentamers



Erick Lima¹, Rulong Ma^{2,3}, Greg Morrison^{2,3}

¹Department of Mathematics, Lone Star College Cy-Fair, Cypress, TX 77433

²Department of Physics, University of Houston, Houston, TX 77204, USA

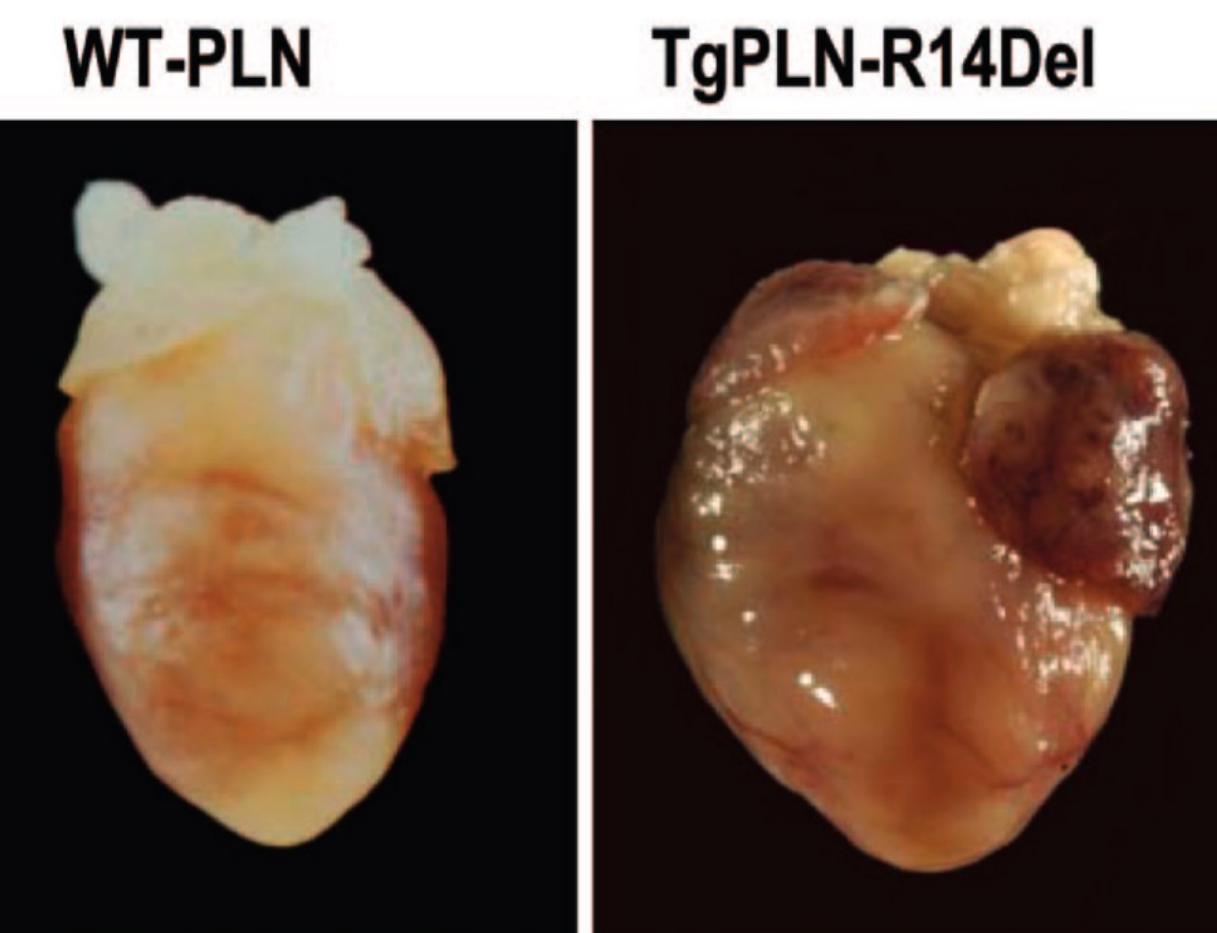
³Center for Theoretical Biological Physics, Rice University, Houston, TX 77005, USA



RICE

Background

- Phospholamban (PLN) regulates calcium uptake into the SR via SERCA → critical for cardiac contraction/relaxation.
- R14del mutation causes familial dilated cardiomyopathy by disrupting Ca^{2+} homeostasis.
- Goal: Determine how R14del alters pentamer stability and dynamics using MD simulations.



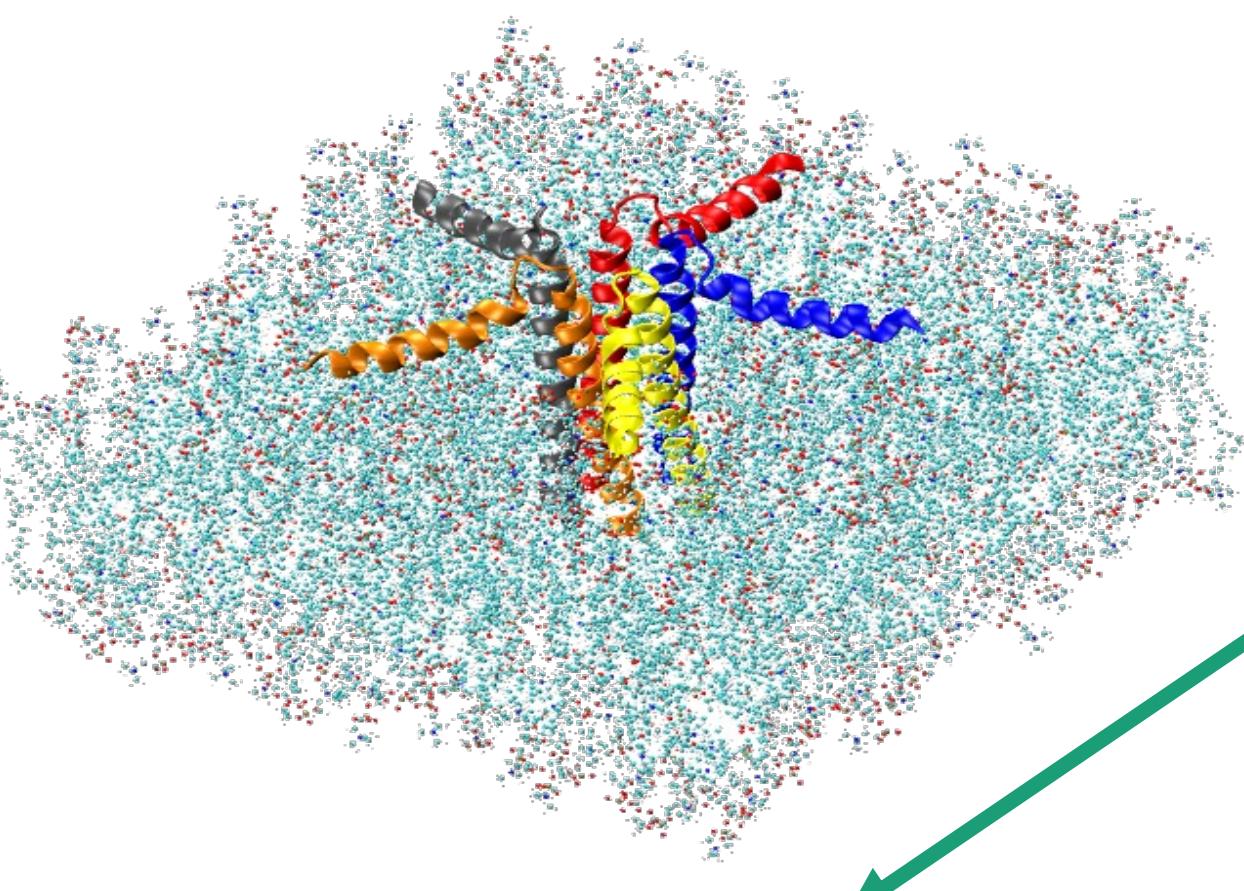
Methods

- Unbiased atomistic Molecular Dynamics simulation
- Software: NAMD, VMD, CHARMM-GUI, HOLE, MDanalysis, Rstudio.
- Conditions: lipid DOPC ($12 \text{ nm} \times 12 \text{ nm} \times 9.4 \text{ nm}$), 0.15 M NaCl, 310 K, NPT ensemble

Workflow

MD Simulations of PLN Pentamers

- System Preparation**
- Built WT and R14del PLN pentamers in $120 \times 120 \text{ \AA}$
 - Solvate and Ionize system



- Molecular Dynamics Simulation**
- Run $3 \times 1 \mu\text{s}$ unbiased simulations (WT & R14del)
 - Capture structural dynamics under physiological conditions

- Trajectory Processing**
- Align frames to reference
 - Clean and prepare trajectories for analysis

- Structural and Functional Analysis**
- Global Stability: RMSD & Helix Tilt
 - Local Flexibility: RMSF
 - Functional Geometry: Pore Radius Profiles

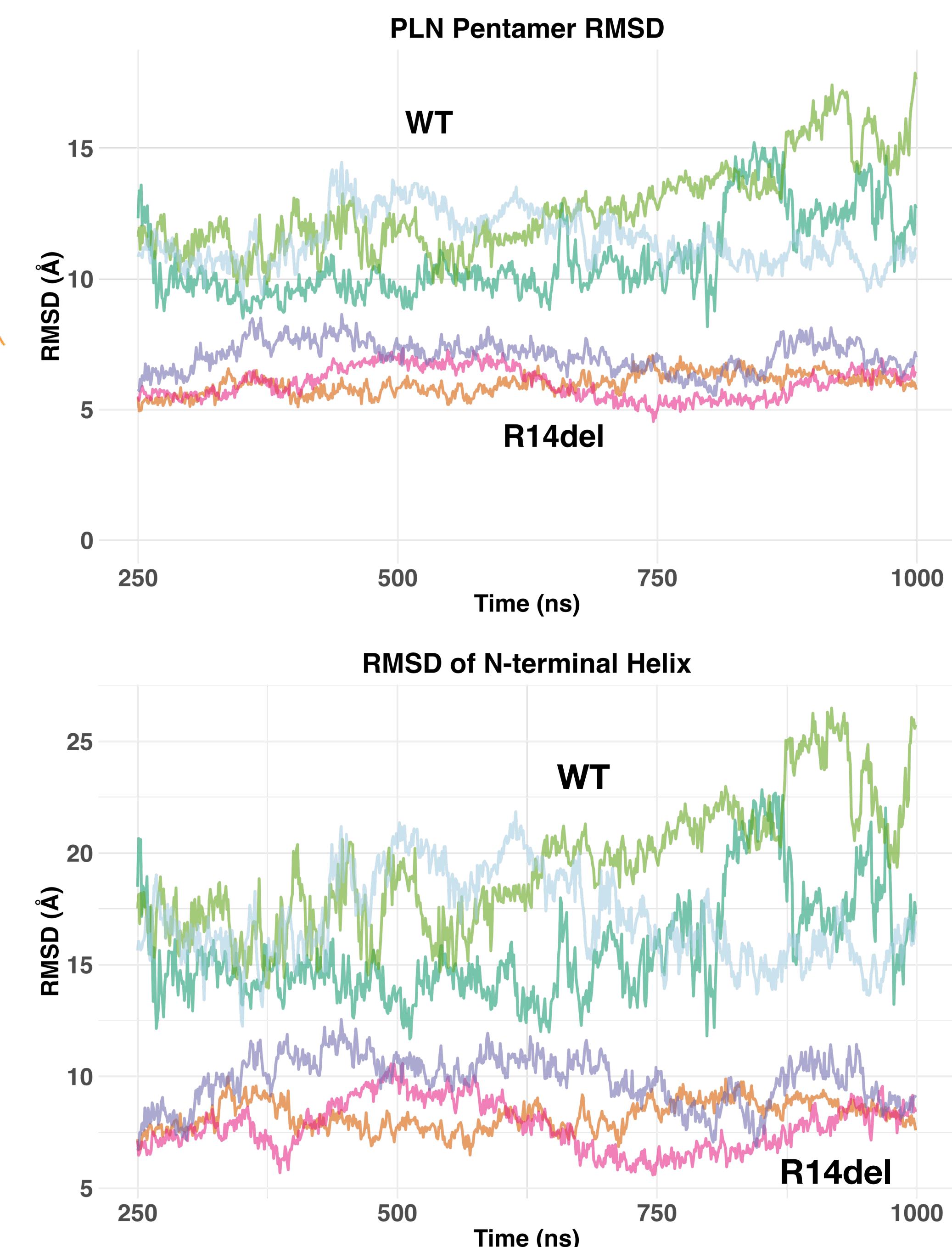
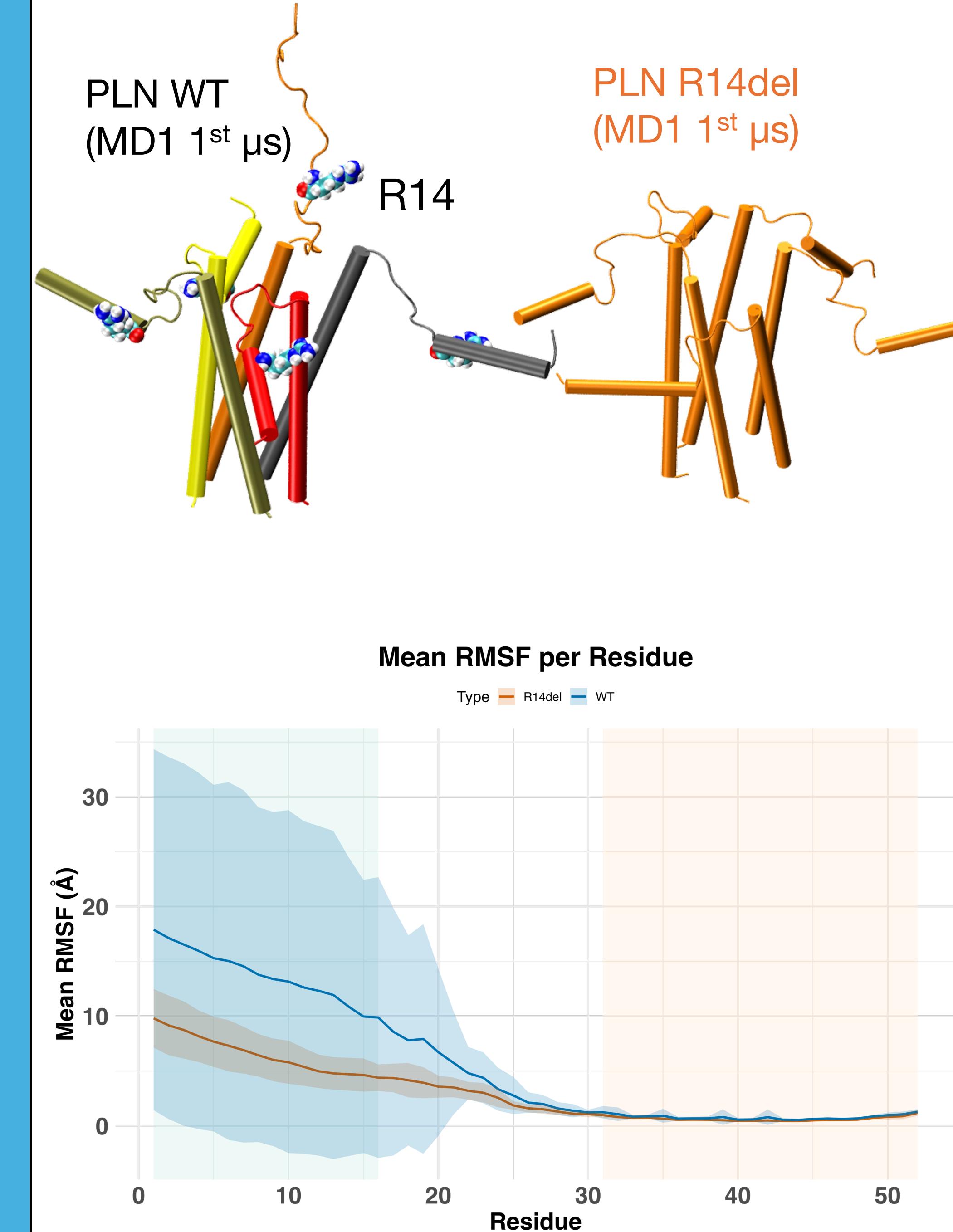
- Biological Interpretation**
- R14del stabilizes pentamers
 - Reduces free monomer PLN
 - Reduces SERCA regulatory dynamics
 - Supports potential DCM pathogenesis

References:

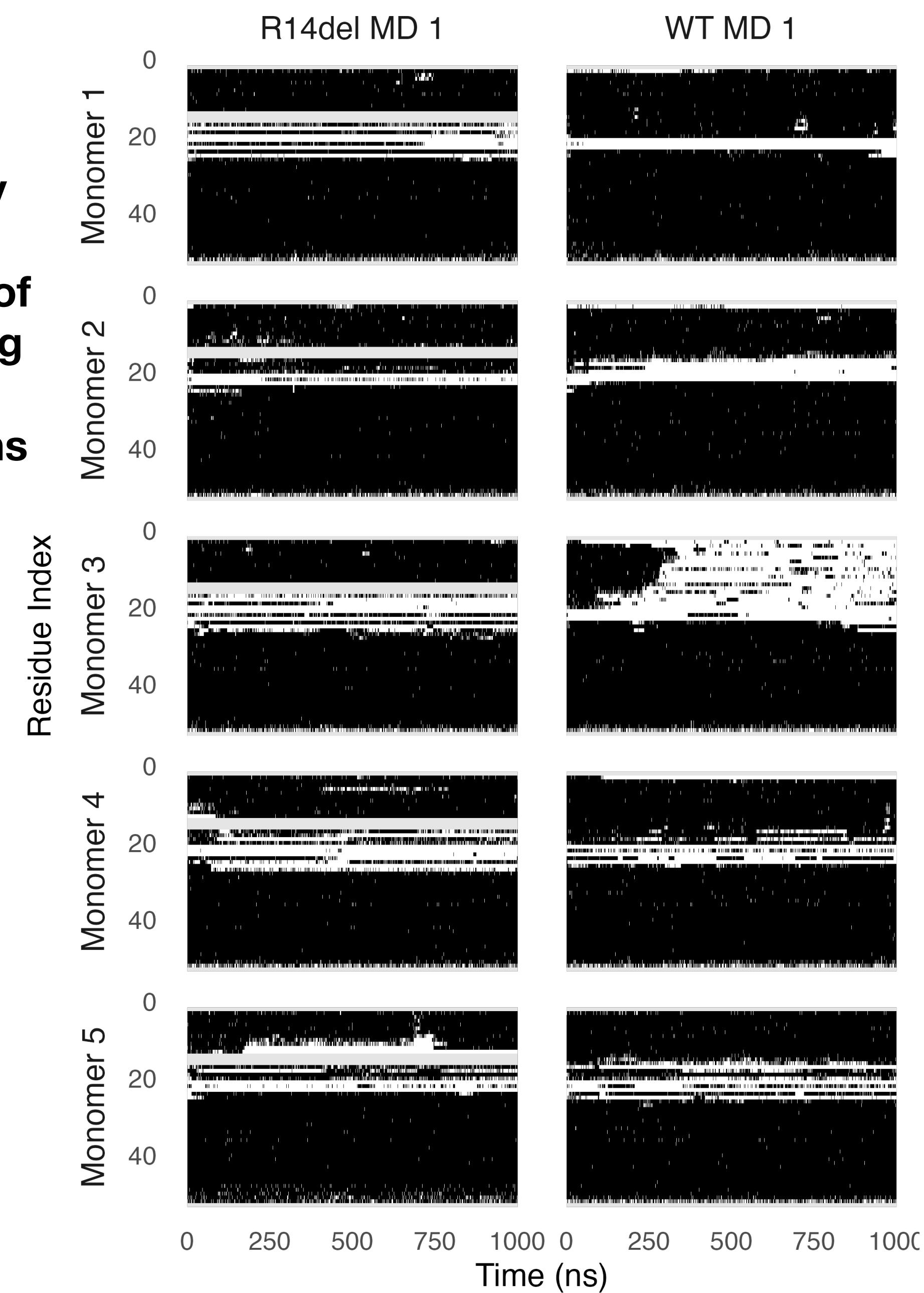
- [1] Verardi R, et al. Proc Natl Acad Sci USA 108, 9101–9106 (2011).
- [2] Haghghi K, et al. Proc Natl Acad Sci USA 103, 1388–1393 (2006).
- [3] Stege NM, et al. JACC Basic Transl Sci 9, 1041–1052 (2024).
- [4] Cleary SR, et al. J Biol Chem 301, 108118 (2025).
- [5] Michaud-Agrawal N, et al. J Comput Chem 32, 2319–2327 (2011).
- [6] Humphrey W, et al. J Mol Graph 14, 33–38 (1996).
- [7] Phillips JC, et al. J Comput Chem 26, 1781–1802 (2005).
- [8] Jo S, et al. J Comput Chem 29, 1859–1865 (2008).

Results

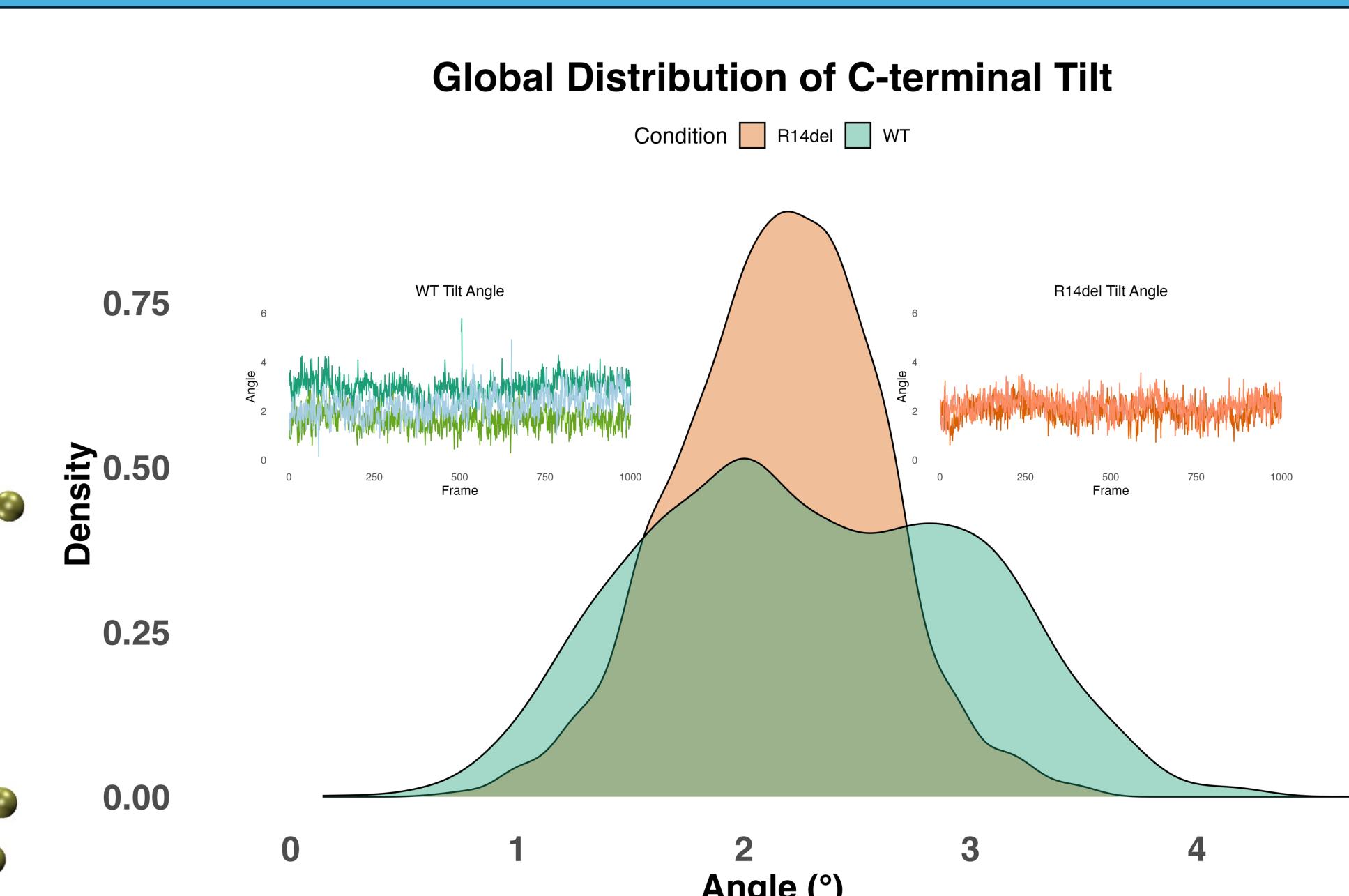
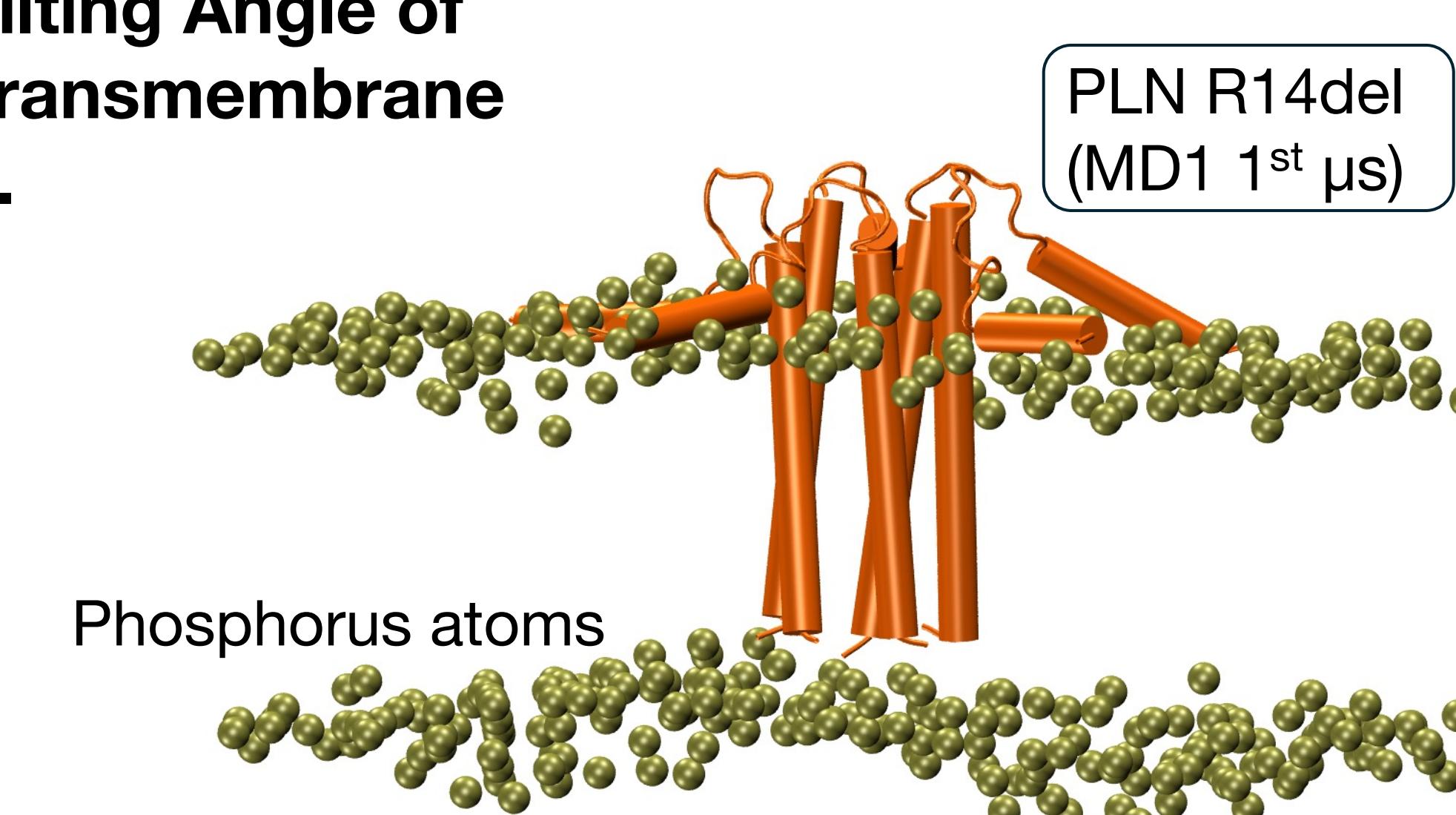
Result 1: R14del Mutation Increases Structural Stability of PLN in MD Simulations.



Result 2: R14del Mutation Stabilizes the N-Terminal Helix structure of PLN.

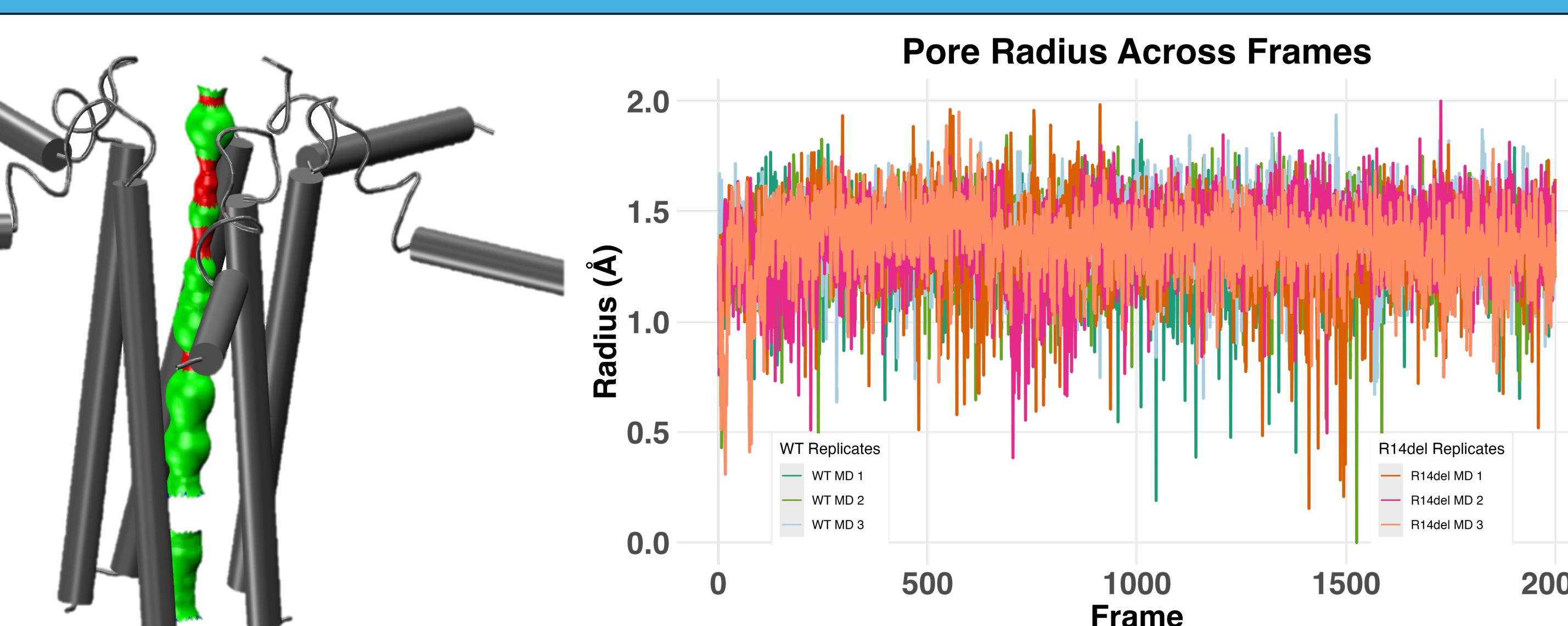


Result 3: R14del Mutation Stabilizes the Tilting Angle of the Transmembrane Helix.



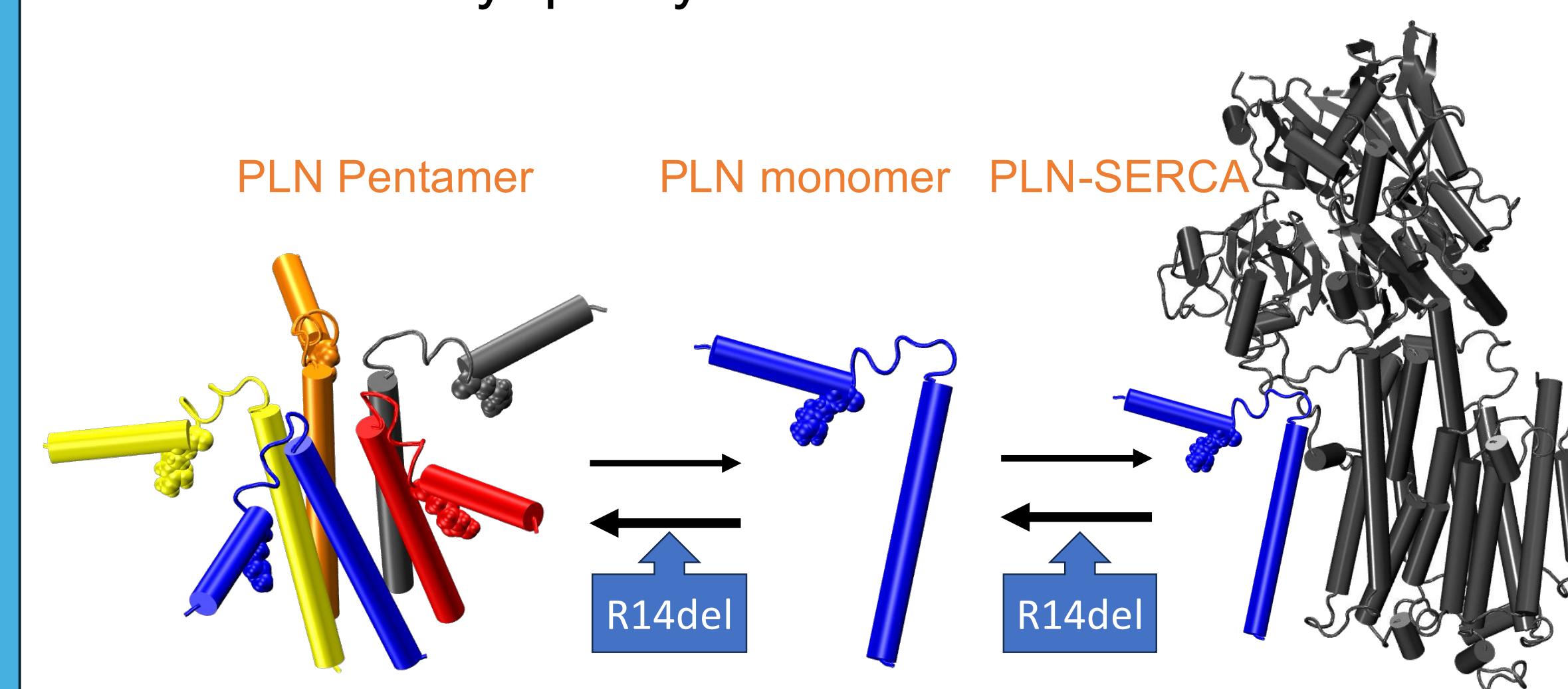
Result 4: R14del Mutation Has Minimal Effect on Pore Radius During Short MD Simulations.

PLN WT (PDB)



Conclusion

R14del stabilizes PLN pentamers, reducing N-terminal mobility and overall structural fluctuations without altering pore geometry. This increased rigidity likely impairs the dynamic regulatory function of PLN, providing a structural basis for its pathogenic role in dilated cardiomyopathy.



Acknowledgements:

The ORBITS program was funded by NSF-PHY-2019745. This work was completed with resources provided by the Research Computing Data Core at the University of Houston.

