Different terminal capping of tau PHF6 displays distinct effects on the structural stability of membrane-bound PHF6 fibril and fibril-induced membrane disruption

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1 | Introduction

Abnormal aggregation of tau into amyloid fibrils is closely linked to Alzheimer's disease and other neurodegenerative diseases [1]. Tau interacting with membranes is experimentally reported to promote protein fibrillization and disrupt membrane integrity [2], thus causing neurotoxicity. The hexapeptide PHF6 is the crucial fibril-nucleating core and widely serves as a model system to study the aggregation of tau proteins [3], while the effect of terminal capping on its interaction with membranes and the underlying mechanisms remain elusive. Herein, we perform extensive all-atom molecular dynamics simulations to investigate the interactions between four capping variants of PHF6 fibrils and membranes, as well as the resulting fibril stabilization and membrane disruption.

2 | Materials & Methods

Four capping variants of PHF6 peptides:

System 1: Ac-PHF6

System 2: Ac-PHF6-NH_2

System 3: PHF6

System 4: PHF6-NH_2

System: Fibril | Fibril + Membrane

Method: MD in NPT ensemble, 1 μs

Force Field: AMBER99SB-ILDN

3 | Results

■ **The fibrillar structures of PHF6 capping variants display different stability in solution**

Ranking of stability:
Ac-PHF6-NH_2>Ac-PHF6 >>>PHF6~PHF6-NH_2
(2>1>>>3~4)

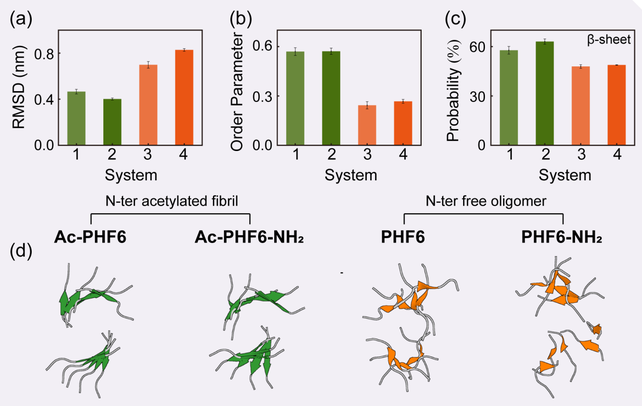

Fig. 1. Structural stability of four performed PHF6 fibrils in solution.

■ **The structural stability and order of all capping variants increase in the presence of membrane**

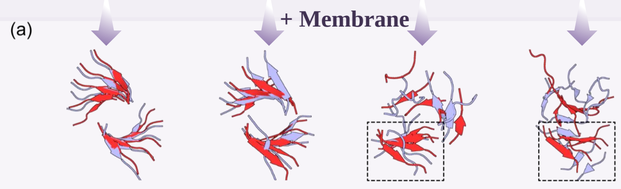

Fig. 2. Comparison of fibril stability in solution (blue) and in the membrane environment (red).

System		RMSD (nm)	β-sheet probability (%)	Order parameter
Ac-PHF6	\	0.4660 ± 0.0007	57.8 ± 3.2	0.5695 ± 0.0996
	+membrane	0.3729 ± 0.0006	60.2 ± 2.5	0.5715 ± 0.0822
Ac-PHF6-NH_2	\	0.4020 ± 0.0007	63.1± 2.6	0.5715 ± 0.0848
	+membrane	0.3556 ± 0.0005	63.5 ± 1.4	0.6352 ± 0.0597
PHF6	\	0.6986 ± 0.0007	47.9 ± 4.9	0.2430 ± 0.0858
	+membrane	0.5872 ± 0.0004	54.4 ± 2.5	0.3043 ± 0.1568
PHF6-NH_2	\	0.8281 ± 0.0033	48.8 ± 4.7	0.2669 ± 0.0689
	+membrane	0.6000 ± 0.0017	49.8 ± 2.6	0.3817 ± 0.1736

Table 1. Stability for each capping variant of $Tau_{306-311}$ fibril in the absence/presence of membrane.

■ **N-ter acetylated: similar improvement in stability of each protofibril and the enhanced interaction between paired β-sheets**

■ **N-ter non-acetylated: a single layer is significantly stabilized but the interlayer interaction is weakened.**

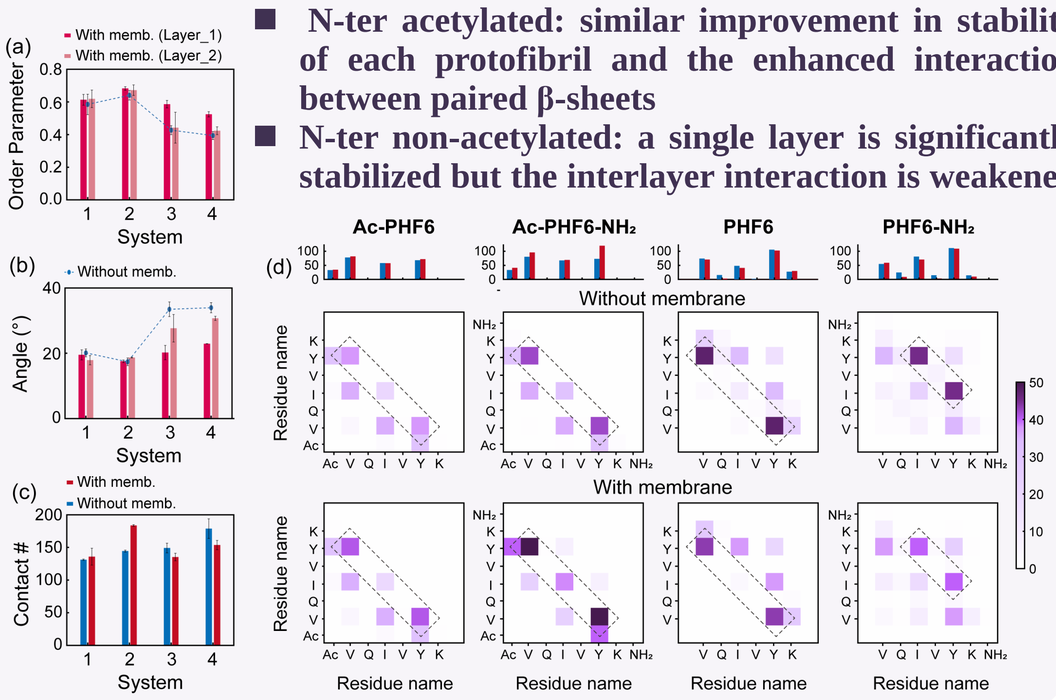

Fig. 3. Analysis of structural stability of each β-sheet layer and the interlayer interactions.

Fibril/Protofibril *Stabilize*

■ **N-terminal modification determines the *Distinct Binding Modes* of PHF6 on lipid bilayers**

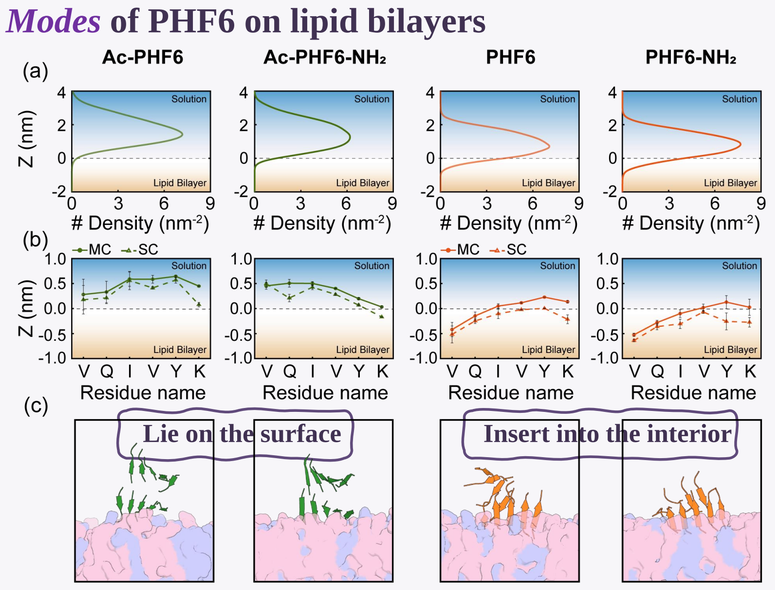

Fig. 4. Binding modes of proteins to membranes in the four systems.

■ **Mechanism: the additional salt-bridges formed between free N-termini and lipid molecules**

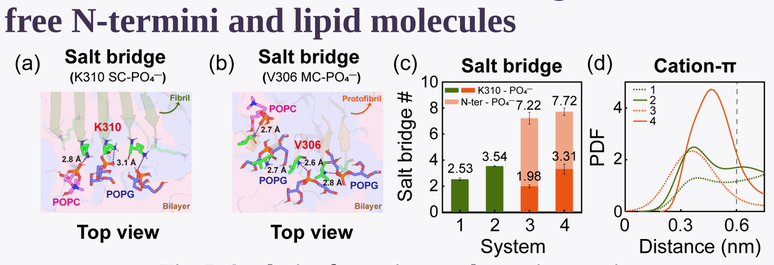

Fig. 5. Analysis of protein-membrane interactions.

Disrupt *Membrane*

■ **Distinct fibril-membrane interactions result in varying degree of membrane thinning and lipid packing disruption.**

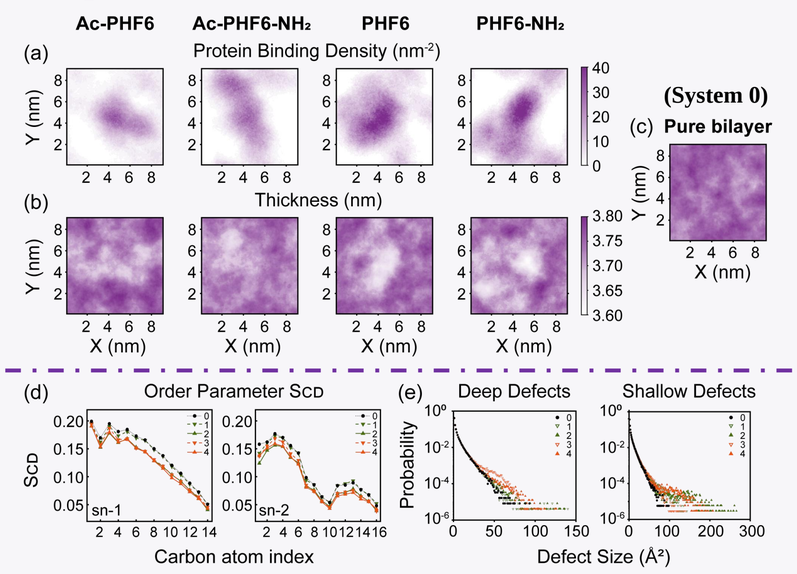

Fig. 6. Influence of protein binding on structural properties of lipid bilayers.

4 | Conclusion

Our simulations emphasize the pivotal role of N-terminal capping in modulating the fibril-membrane binding. N-terminal acetylated fibrils bind on the bilayer surface primarily through lysine-lipid electrostatic attraction, leading to the increased stability of global fibril structures and localized membrane disturbance. Meanwhile, the binding modes of N-terminal free systems, characterized by peptide N-termini inserting into membranes, result in significant stabilization of a single β-sheet layer and more severe membrane disruption.

5 | References

[1] Fitzpatrick, Anthony WP, et al. *Nature* 547.7662 (2017): 185-190.

[2] Fanni, Adeline M., et al. *Journal of Biological Chemistry* 294.42 (2019): 15304-15317.

[3] Pretti, Evan, and M. Scott Shell. *Proceedings of the National Academy of Sciences* 120.48 (2023): e2309995120.