Modeling Huntington's Disease Using Molecular Dynamics Simulations

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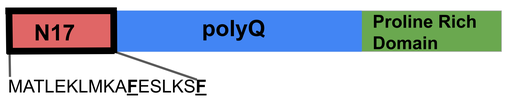
Abstract

Huntington's Disease is a fatal neurodegenerative disease caused by abnormal aggregation of the Huntingtin protein (*htt*) in neurons, primarily led by the N17 domain. Research shows that N17 preferentially binds to regions of curvature on a lipid bilayer, but its mechanism is unknown. Coarse-grained molecular dynamics simulations allow insight into these curvature-sensing mechanisms. It was found that modulating the electrostatics of the lipid bilayer affects the ability of N17 to sense curvature. Other preliminary results show that mutating phenylalanine residues on N17 causes changes in curvature sensing. Thoroughly understanding the mechanisms of N17 and its electrostatic properties will hopefully bring researchers closer to uncovering therapeutics for Huntington's.

Introduction

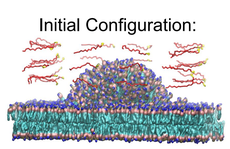
- Huntington's disease (HD) is a neurodegenerative disease caused by the abnormal expansion of the polyQ domain (repeats of the amino acid glutamine) of the Huntingtin protein (Htt):

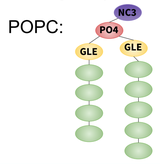


- This structure leads to increased aggregation and neurotoxicity.
- Few studies have explored the interactions between httex1 and lipids.
- N17 is a **membrane binding** domain of httex1 that anchors the protein and promotes aggregation[1] of the polyQ region.
- The htt protein, particularly the N17 domain, has been shown[2] to **sense and preferentially bind to regions of curvature,** with deep insertion of **hydrophobic phenylalanine (PHE)** sidechains.
- Coarse-grained molecular dynamic simulations can allow insight into the curvature-sensing mechanisms of the htt protein, which are computationally unattainable using all-atom simulations.

Methods

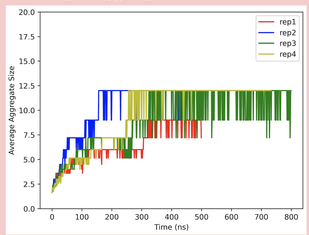
- Using **GROMACs simulation engine**, 36 N17 peptides were allowed to interact with a neutral, hemispherical-planar membrane (POPC) for as long as 500-800 nanoseconds.
- To **modulate hydrophobic effects**, PHE residues were mutated to MET, a smaller hydrophobic residue, thus producing 2 mutants: $N17^{F11M}$ and $N17^{F17M}$.
- To **modulate electrostatics**, N17 interacted with a 100% anionic lipid bilayer (POPS).



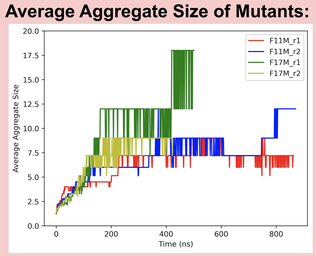


Lipid Composition	N17 binding to curved	N17 binding to planar
100% POPC	77.5%	22.5%
100% POPS	31%	67.86%

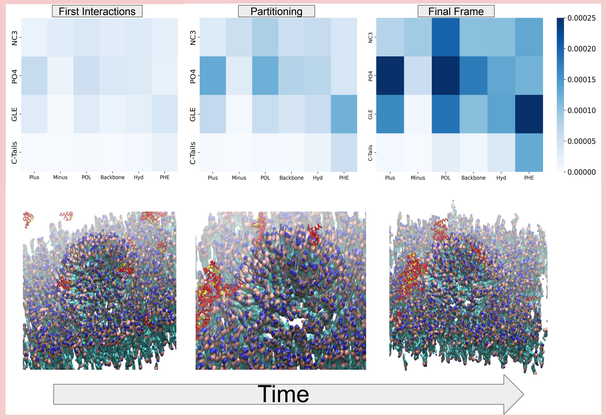
Average Aggregate Size of N17:



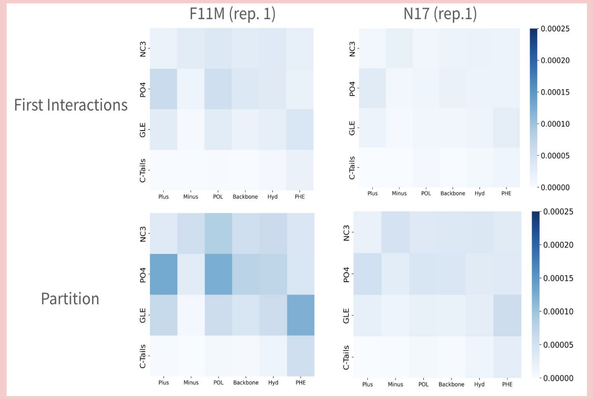
Average Aggregate Size of Mutants:



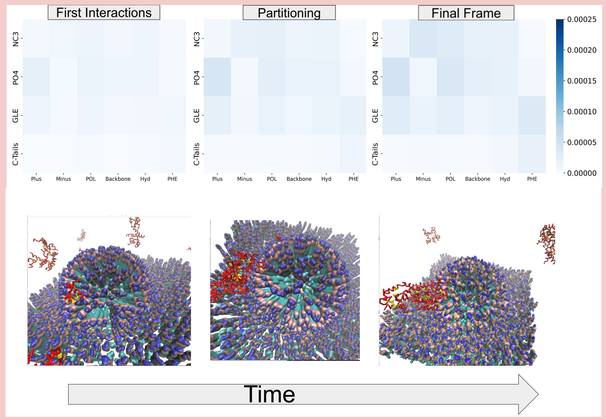
Contact Map of $N17^{F11M}$ In 100% POPC:



Comparing Contact Maps of N17 to $N17^{F11M}$ in 100% POPC:



Contact Map of $N17^{F17M}$ In 100% POPC:



Results

- A 100% anionic lipid system (POPS) results in the the loss of curvature-sensing
- $N17^{F17M}$ produces bigger aggregates compared to the N17 and $N17^{F11M}$.
- Contact maps indicate differences in peptide-lipid interactions, where darker colors indicate stronger interactions.
- $N17^{F11M}$ has more direct contacts with the curved membrane compared to $N17^{F17M}$.
- Removal of PHE ($N17^{F11M}$) results in more direct contacts with the curved region compared to N17 (first replicates).

Conclusions

- **PHE drives the curvature sensing** of N17.
- Modulating the electrostatics of the lipid can result in loss of curvature-sensing.
- **Balance between the electrostatics and hydrophobic effects** is crucial in curvature-sensing.
- Variants of N17 behave differently in terms of aggregation and interactions with the curved membrane.
- Removal of PHE leads to more direct contacts with the curved membrane.

Future Directions

- Run analysis on interpeptide PHE-PHE contacts of $N17^{F11M}$ and $N17^{F17M}$ over time.
- Run simulations for longer (~1000 nanoseconds).
- Run more replicates using similar analysis.

References

1. Zheng, Z., Li, A., Holmes, B. B., Marasa, J. C., & Diamond, M.I. J. Biol. Chem. (2013)
2. Chaibva, M., Burke, K. A., & Legleiter, J. Biochemistry. (2014)
3. Boyd, K.J., & May, E. R. J. Chem. Theory Comput. (2018)

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