Multiscale simulation of Polyglutamine oligomerization

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Abstract

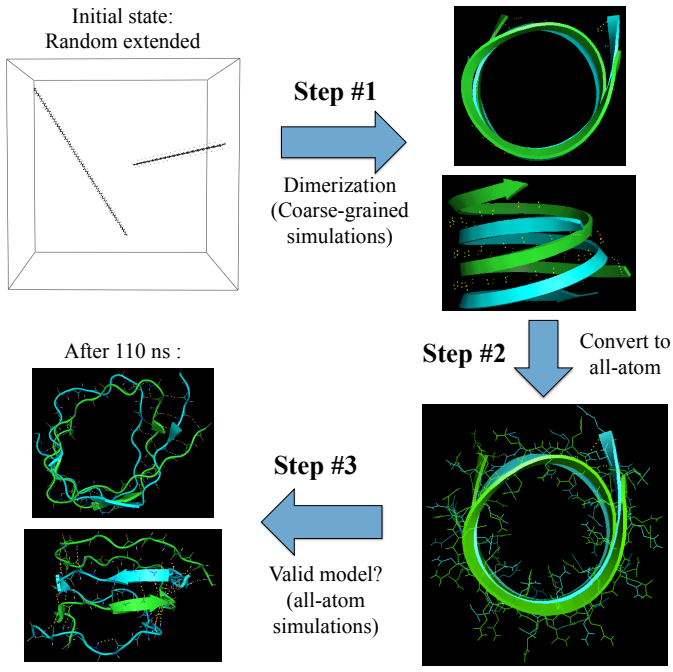
- Many neurodegenerative diseases, such as Huntingdon's, are related to the Polyglutamine (PolyQ) repeat disorder.[1] In Huntingdon's, the huntingdin protein is incorrectly produced with a consecutive segment of amino acids of more than 35 glutamines:

Wildtype sequence: MATLEKLMKA FESLKSQQQQ QQQQQQQQQQ QQQQQQQQPP PPPPPPPPPQ LPQPPQAQPL ••• TCLRNVHKVT

If > 35 Q => pathological

- This protein then folds incorrectly inhibiting its physiological function.
- Many experiments investigated the folding of the PolyQ segment alone and several models, often contradictory, were proposed[2,3].
- It is not clear which of these models are relevant and the morphologies of small oligomers of PolyQ are still unknown at the molecular level.
- Here, we investigate the folding of PolyQ40 using a multiscale simulation. We also look at the effect of the chain length (PQ30, PQ35 and PQ37) on oligomerization.

Multiscale simulation protocol



- **Step #1:** Simulate the folding of PolyQ using the coarse-grained potential OPEP coupled to the sampling algorithm T-REMD[4]. From these simulations, we obtained a stable nanotube-like topology for the dimer of PolyQ37 and PQ40, but not for PQ30 and PQ35.
  - Coarse-grained simulations can reach longer time-scales and provide better sampling and thermodynamics.
- **Step #2:** Convert the coarse-grained nanotube morphology to all-atom using SCRWL4[5], which reconstruct the side-chains from the backbone conformations.
- **Step #3:** Simulate the all-atom nanotube using GROMACS 4.5.4[6] with OPLS AA[7] and TIP4P water in NPT ensemble (300K, 1 atm). Confirm its stability.
  - All-atom simulations complement Step #1 by providing information on the role of water; and side-chains H-bonds and packing.

Financing

NSERC CRSNG
GEPROM
Université de Montréal

Results

- The nanotube composed of two PolyQ40 chains is metastable. (See figure 1, **red** curve)
- Therefore, we decided to investigate the stability of a longer nanotube composed of 3 shorter nanotubes stacked above each other. This new structure is very stable even after 250 ns. (See figure 1, **black** curve)
- In the longer nanotube topology, the middle subunit is very stable with small fluctuations. (See figure 1, **blue** curve and figure 2, **black** curve vs. **red** curve)

Final structure after 250 ns:

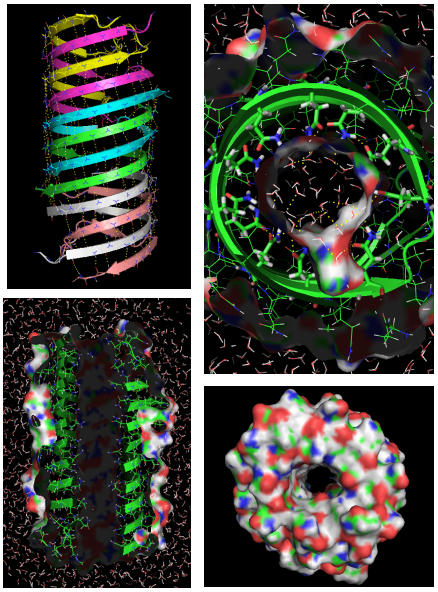


Figure 1 - Backbone-RMSD versus initial conformation

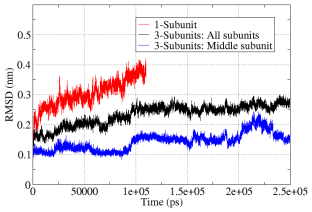
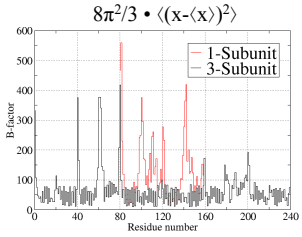
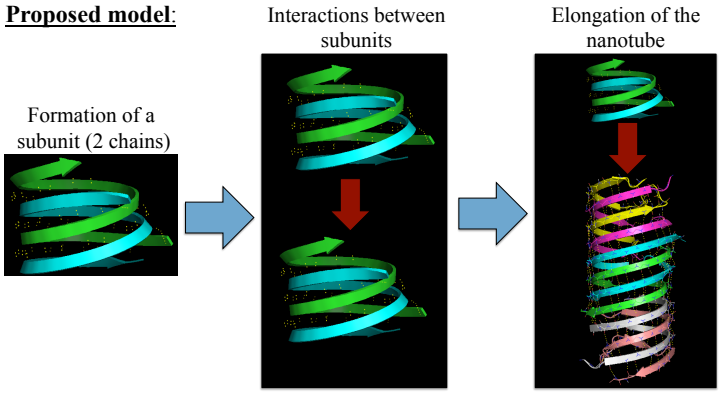


Figure 2 - B-factors: $8\pi^2/3 \bullet \langle(x-\langle x\rangle)^2\rangle$



Note: 81-160 corresponds to the middle subunit in the longer nanotube (3-Subunit)

Proposed model:



Conclusion

- The nanotube composed of two PolyQ40 chains is metastable and it can be used as a building block to form a longer nanotube that is significantly more stable.
- Main-chain H-bonds and H-bonds between glutamine side-chains (NH_2 and O groups) and water is crucial to the stability of the nanotube structure.
- **Now**, we are simulating the further polymerization of the nanotube using our coarse-grained approach to validate the model proposed above.
- Also, we are currently investigating the stability of the nanotube made by shorter chain (PQ30 and PQ35) using all-atom MD simulations.

1 – Bauer, P.O. et al., The pathogenic mechanisms of Polyglutamine diseases and current therapeutic strategies, *J. Neurochem.* **2009,** *110,* 1737-1765.
2 – Takahashi, T. et al., PolyQ diseases: where does toxicity come from? What is toxicity? Where are we going?, *J. Mol. Cell. Biol.* **2010,** *2,* 180-191.
3 – Perutz, M.F. et al., Amyloid fibers are water-filled nanotubes, *PNAS* **2002,** *99,* 5591-5595.
4 – Laghaei, R. et al., Spontaneous formation of Polyglutamine nanotubes with molecular dynamics simulations, *J. Chem. Phys.* **2010,** *132,* 165102.
5 – Krivov, G.G. et al., Improved prediction of protein side-chain conformations with SCWRL4, *Proteins* **2009,** *77,* 778-795.
6 – Hess, B. et al., GROMACS 4: Algorithms for highly efficient, load-balanced and scalable molecular simulation, *JCTC* **2008,** *4,* 435-447.
7 – Kaminski, G.A. et al. Evaluation and Reparametrization of the OPLS-AA Force Field for Proteins, *J. Phys. Chem. B* **2001,** *105,* 6474-6487.