Fibril-like conformation of Aβ42 monomer in water and interaction of D3-peptide with the Aβ42 monomer

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Introduction

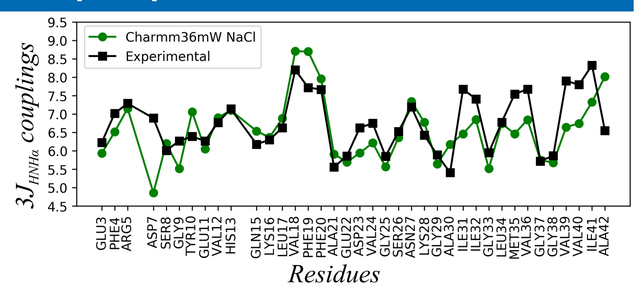
Amyloid β protein 1-42 (Aβ42) has a complex aggregation process that involves a combination of primary and secondary nucleation as well as fibril elongation. The basic aggregation unit is the monomeric peptide characterized by a high conformational flexibility. Recent experimental studies have revealed a random coil behaviour of the Aβ42 monomer which we confirm here with molecular dynamics (MD) simulations. Furthermore, we identify a conformation with C-terminus structure resembling that of fibrilar peptides. When combined with an enantiomeric D-peptide which has been shown to inhibit the Aβ42 aggregation into toxic oligomers, the Aβ42 monomer and the D-peptide bind non-covalently via a weak exhotermic reaction, dominated by the entropic component. This behaviour has been observed experimentally and we confirm it computationally in this work. We also identify a binding mode dominated by electrostatic and polar interactions.

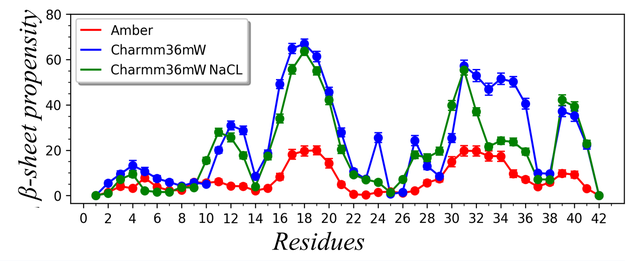
Methods

- Hamiltonian replica exchange molecular dynamics (H-REMD)
- Gromacs 2016.04 [1] and Plumed 2.4.1 [2]
- All atom MD simulations of the Aβ42 monomer using:
  1. Amber99SB*-ILDN [3] and the TIP4PD water - 2 μs/replica [4]
  2. Charmm36m and the TIP3P water - 2 μs [5]
  3. Charmm36mW and the TIP3P water - 3 μs [5]
  4. Charmm36mW, the TIP3Pwater and 150 mM NaCl - 4.6 μs
- Aβ42 monomer with D3-peptide simulations using: Charmm36mW, the TIP3P and 50 mM NaCl - 1 μs

Aβ42 monomers - general properties

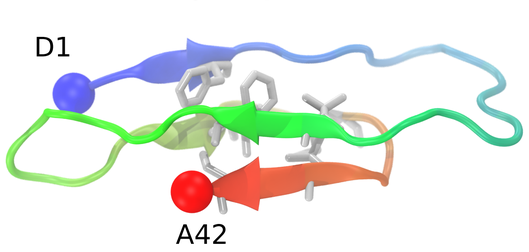
- Monomers adopt random coil conformations
- $3J_{HNH\alpha}$ NMR couplings with Charmm36mW and NaCl give the best correlation with experimental values [6] (reduced $\chi^2 = 2.7$)
- Metastable conformations with β-sheet structure are frequent

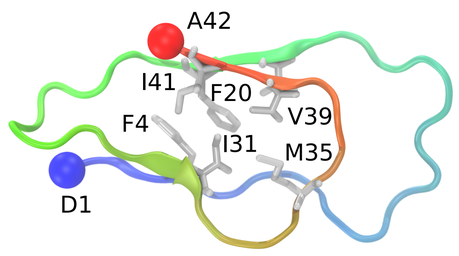




Metastable conformation with Charmm36mW

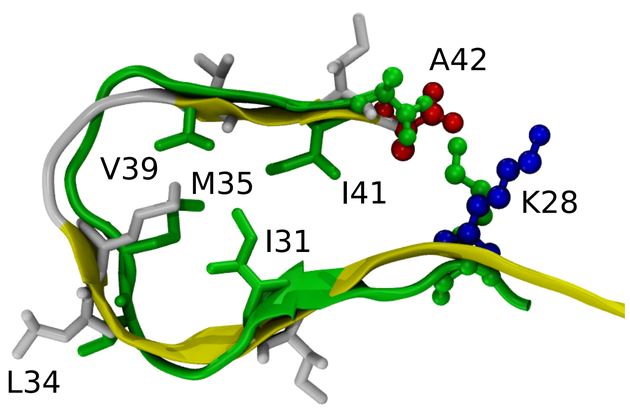
- Clustering of all conformations with Daura method and cutoff of $0.4\ nm$
- Center of largest cluster
- C-terminal hydrophobic residues shielded from solvent



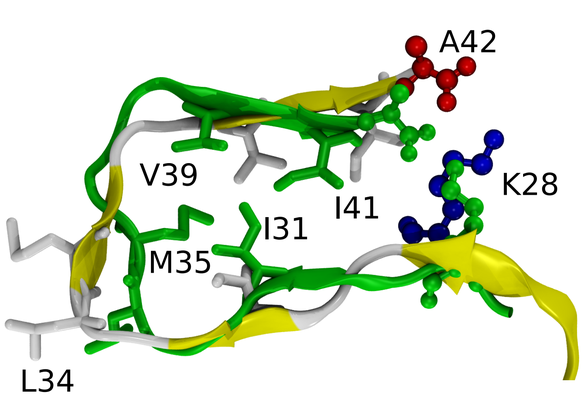


Comparison to fibril models

- Cryo-EM fibril, pH of 2 [7]
- Solid state NMR fibril, pH of 7.4 [8]



$RMSD_{C\alpha} = 0.21\ nm$



$RMSD_{C\alpha} = 0.25\ nm$

Binding of D3-peptide to Aβ42 monomer

- D3 enantiomeric peptide sequence: ***rprtrlhthrnr***
- Binding probability P_b calculated based on the minimum distance
- The dissociation and association constants are obtained from P_b

$$K_D = 1/K_A = (1 - P_b)/P_b * C/C_0,$$

where C is the concentration in the simulation and C_0 is a standard concentration of $1M/L$

- The Gibbs free energy is obtained from K_D

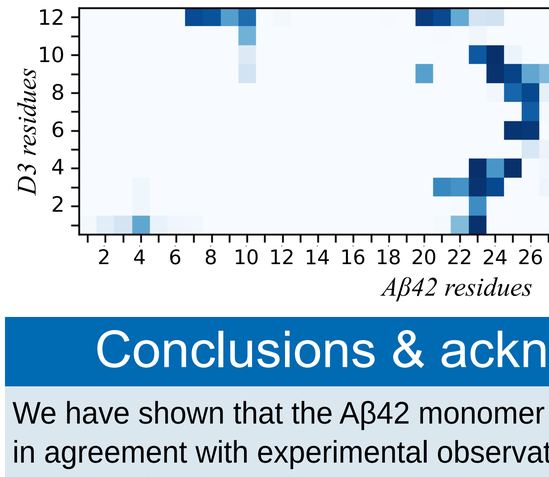
$$\Delta G_o = RTln(K_D),$$

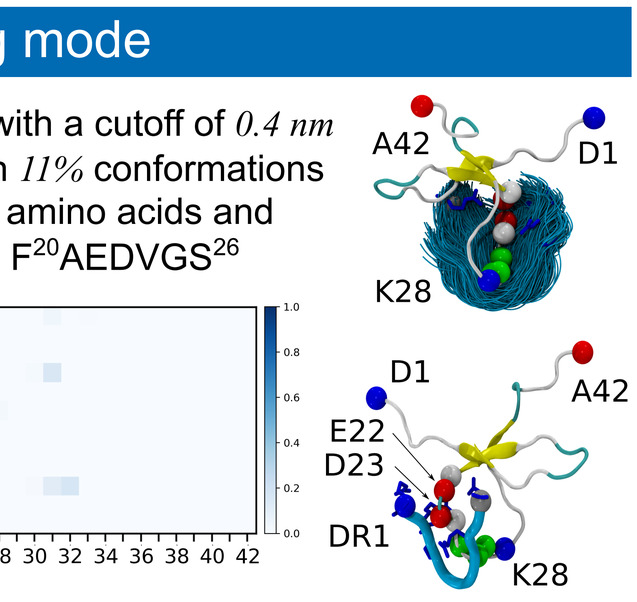
where R is the gas constant and T is the simulation temperature

- The effective temperatures of H-REMD replicas are determined [9]
- The binding entropy and enthalpy are obtained from van't Hoff plots

Thermodynamics of interaction

- A van't Hoff plot shows the changes in the dissociation constant as a function of inverse temperature
- The slope is proportional with ΔH_o *and the intersection value at* $1/T = 0$ with $(-T\Delta S_o)$





- Thermodynamic properties from simulation and experiment [10]

Method	$\Delta G_o[kJ/mol]$	$\Delta H_o[kJ/mol]$	$-T\Delta S_o[kJ/mol]$
Simulation	-19.2 ± 0.5	-5.3 ± 4.0	-14.1 ± 3.1
Experiment	-26.6 ± 2.9	-4 ± 0.8	-23 ± 3.0

Representative binding mode

- The largest cluster calculated with a cutoff of $0.4\ nm$
- This binding mode is present in 11% conformations
- Main contacts are between D3 amino acids and Aβ42 sequences D^7SGY^{10} and $F^{20}AEDVGS^{26}$

Conclusions & acknowledgments

We have shown that the Aβ42 monomer adopts a random coil conformation in water, in agreement with experimental observations, while often expressing β-sheet structure at certain locations along the sequence. In addition, we have observed a compact metastable monomer conformation with fibril-like C-terminus structure. This conformation is very relevant for the fibril elongation process by monomer addition.
Replica exchange simulations of Aβ42 monomer with D3-peptide reproduce interaction thermodynamics observed in experiment. By using the inverse temperature dependence of the dissociation constant we calculated standard binding free energy, enthalpy and entropy. The values indicate a weak exothermic process mostly entropically driven. The representative binding mode shows strongest interaction between the D3-peptide and the Aβ42 amino acids D7 and D23. These residues are very relevant for AD and are involved in the more aggressive Tottory (D7N) and Iowa (D23N) mutations.

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