The inhibitory mechanism and the size effect of graphene oxide on Aβ(33-42) aggregation -- an atomistic simulation study

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1 | Introduction

Amyloid-β fibril formation has been received considerable attention in the past decades, due to its close association with Alzheimer's disease (AD). Experimental studies[1-2] have indicated that graphene oxide (GO) can efficiently inhibit the self-assembly of the 33-42 fragment of Amyloid-β peptide. Besides, the large size GO shows more effective interaction with Aβ. However, the microscopic mechanism remains elusive. Here, using replica exchange molecular dynamics (REMD) simulations, we investigated the structure of Aβ(33-42) (Aβ for short) tetramer, and the inhibitory mechanism of GO against Aβ(33-42) assembly.

2 | Materials and Methods

Aβ(33-42): **amino acid sequence** ACE-GLMVGGVVIA-NH2
GO: $C_{60}O_{20}H_6$ (GO_{60}) , $C_{120}O_{40}H_{12}$ (GO_{120})
Method: REMD in NPT ensemble, 48 replicas,
pressure: 1 bar , temperature: 307.50-439.37 K, 400 ns
Force Field: Amber99sb-ILDN **Water Model:** TIP3P
Systems: Aβ-tetramer Aβ-tetramer+4GO_{60} Aβ-tetramer+2GO_{120}
Time: 400ns for each REMD simulation
Packages: Gromacs-4.5.3 , VMD and PyMOL

3 | Results

Aβ(33-42) peptides in three systems perform different third structures.

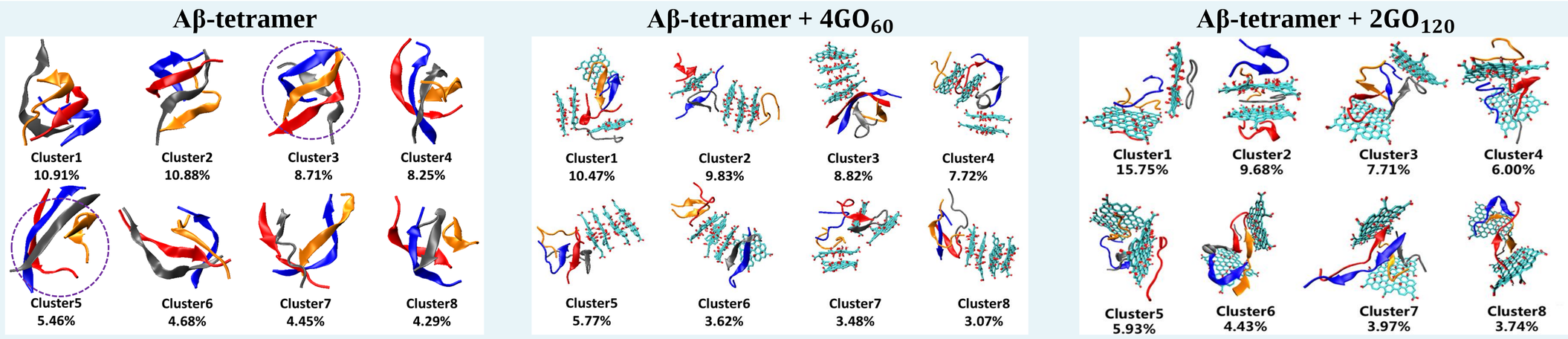

Figure 1. Structure analysis of Aβ-tetramer in three different systems

The Aβ tetramer in the absence of GO has the highest propensity to form β-sheet.

The secondary structure content	Aβ-tetramer	Aβ-tetramer + 4GO_{60}	Aβ-tetramer + 2GO_{120}
β-Sheet	52.27%	22.60%	11.86%
Coil	35.46%	50.56%	54.19%

TABLE 1. The secondary structure content

The ordered conformations of Aβ(33-42) tetramer can be classified into open/closed beta-barrels, curved β-sheets, and extended β-sheets.

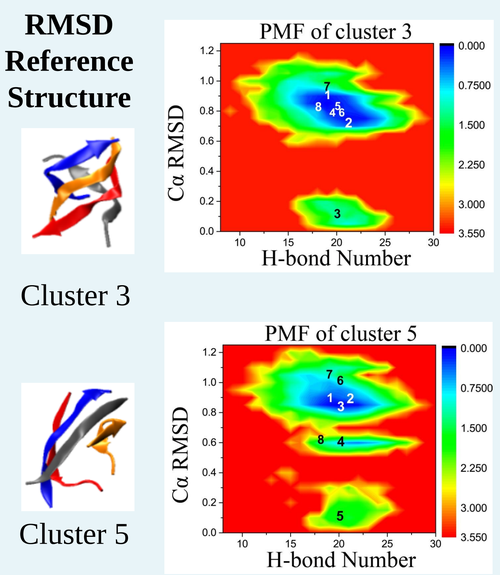

Figure 2. Free energy landscape of Aβ tetramer

Bilayer beta-sheet with six Ab(33-42) peptides as an initial structures can lead to bilayer β-sheet and stable β-barrel structures.

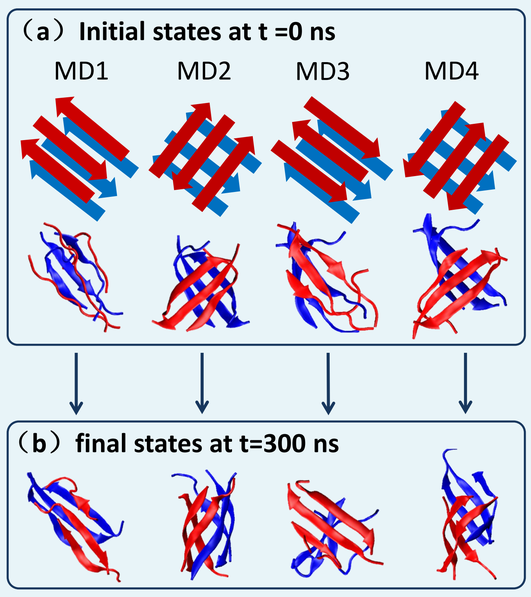

Figure 3. MD study of conformations in cluster 5

Peptides in cluster 3 and cluster 5 mainly adopt aligned/staggered antiparallel orientation. Hydrogen bonds and van der Waals interaction are main interactions.

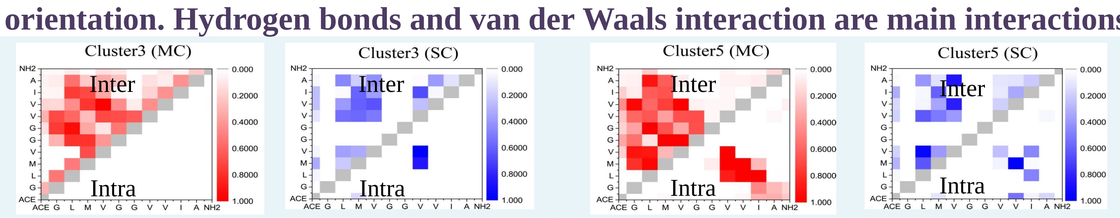

Figure 4. Contact probability maps for cluster 3 and cluster 5

GO inhibits Aβ aggregation, 2GO_{120} has stronger inhibitory effect.

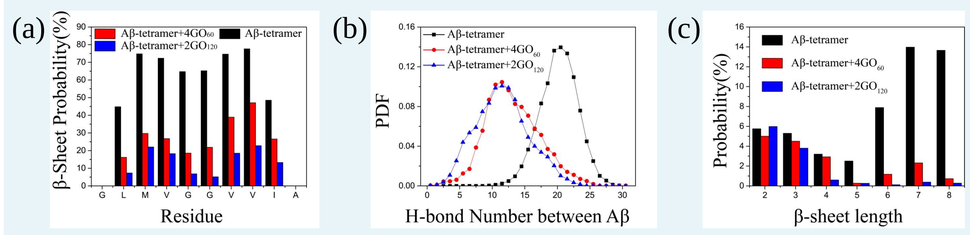

Figure 5. Comparison of β-sheet probabilities (a), Hydrogen bonds number between Aβ (b) and β-sheet length (c) in the three different systems

In the presence of GO, the main chain interaction of peptide become weak and side chain interaction get strong.

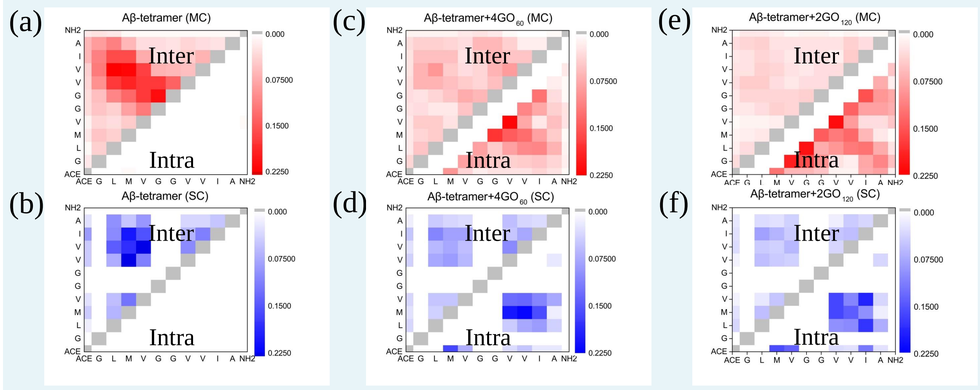

Figure 6. Contact probability maps for Aβ tetramer (a and b), in the presence of 4GO_{60} (c and d) and 2GO_{120} (e and f)

GO can reduce the contact between Aβ by separating and interacting with it, thus inhibits peptide aggregation. Compared to GO_{60}, GO_{120} has stronger interactions with Aβ and stronger separating effect.

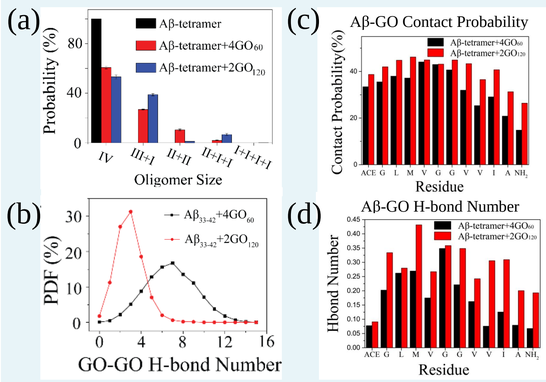

Figure 7. Mechanism of how GO inhibiting Aβ assembly

(a) Oligomer size distributions
(b) The hydrogen bond number distribution between GO molecules
(c) Contact probability of each residue between Aβ and GO
(d) Hydrogen bonds number of each residue between Aβ and GO

4 | Conclusions

We have investigated the structure of Aβ(33-42) tetramer and the effect of GO on Aβ(33-42) assembly by performing extensive REMD simulations. Our simulations show that Aβ(33-42) can form β-barrel and β-sheet structures which have important biological significance. Hydrogen bonds and van der Waals interaction play dominant roles in Aβ(33-42) assembly. GO weakens Aβ-Aβ interactions by separating Aβ from each other, thereby inhibits Aβ oligomerization. Compared to GO_{60}, GO_{120} has better inhibitory effect due to its stronger interaction with Aβ. This study provides molecular mechanism of GO in inhibiting Aβ(33-42) aggregation.

5 | References

1). Li, Q., et al., *Modulating abeta33-42 peptide assembly by graphene oxide.* Chemistry, 2014. 20(24):7236-40.

2). Wang, J., et al., *Size Effect of Graphene Oxide on Modulating Amyloid Peptide Assembly.* Chemistry, 2015. 21(27):9632-7.