Can we improve Coarse-Grained simulations of peptide self-assembly and aggregation by cluster analysis inputs?

Marko Babić[1], Daniela Kalafatović[1]

[1]Faculty of Biotechnology and Drug Development, University of Rijeka

https://doi.org/10.17952/37EPS.2024.P2305

Motivation

Peptide-based nanomaterials have applications in both medicine and industry. Designing accurate molecular dynamics (MD) systems to test supramolecular behavior of peptide assemblies will help develop these materials by providing fast and low-cost screening for new design ideas.

Methods

Three types of atomistic PDB files were generated:
1) **Linear** peptide (standard PyMol output)
2) Conformations from a **cluster** analysis of 10 ns atomistic simulations
3) Top model of a **PEPFOLD3** structure prediction

The structures were converted to Coarse-grained (CG) representatons using the secondary structure flag "E" for the **linear** input, representing an extended beta-sheet conformation. The **cluster** and **PEPFOLD3** generated structures had no secondary structure flags added.
The system was then populated by either 120 or 200 instances of the same deca- or hexapeptide, resprctively. This system was then minimized, equilibrated and run as shown in Figure 1.

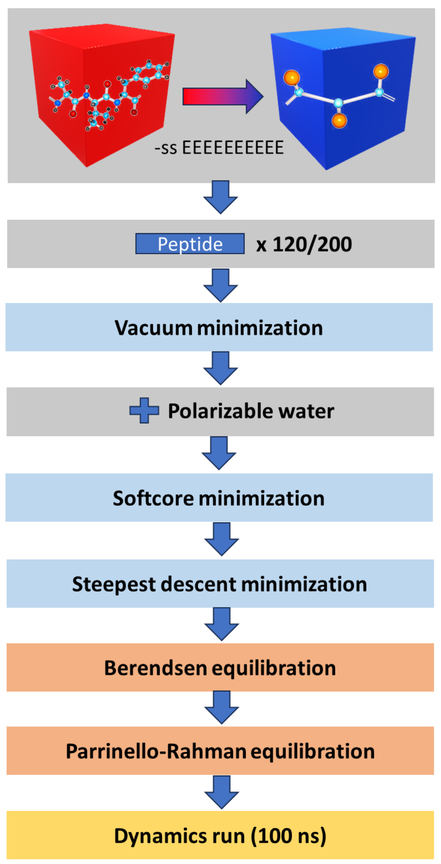

Figure 1 – Showing the method of testing aggregation in molecular dynamics simulattions used in this work.

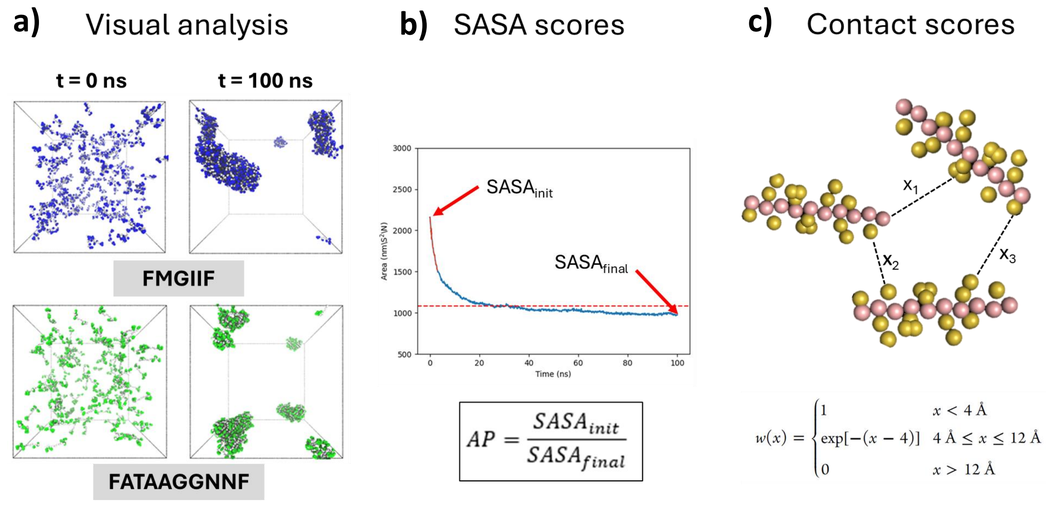

Figure 2 – To prove peptides aggregated 3 tests were done; **a)** a visual analysis of the frames in the simulation. **b)** The AP_{SASA} score is based on solvent accessible surface area (SASA) and its ratio between the first and last frame. **c)** The $AP_{contact}$ score calculates the shortest distances between the peptides, scores them based on the provided formula between 0 an 1, and takes the average score of the last 10 ns of the simulation.

Ramachandran plots were used to obsereve the retention of distinct structural features of the input PDBs. They were made by converting CG files back into all atom systems using the cg2all algorithm and GROMACS for creating the dihedral data that was plotted. The AP_{SASA} and $AP_{contact}$ scores (Figure 2) were compared between peptides to detect the impact of input PDBs, secondary structure flags or both.

Results

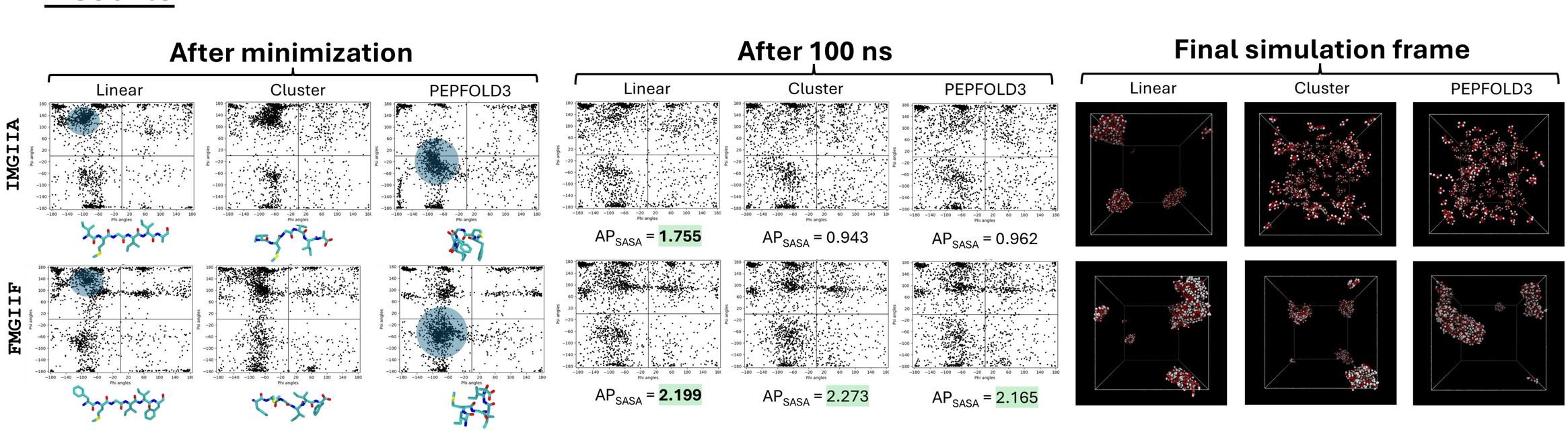

Figure 3 – After minimizing the systems peptides retain their distinct structures. After running the simulations most dihedrals across all systems are similar, regardless of aggregation. The input structures are shown under the Ramachandran plots on the left. On the right, green are marked AP_{SASA} scores indicating aggregation. The final simulation frame provides visual confirmation of aggregation behavior. The two peptides were chosen because of having the smallest (FMGIIF) and largest (IMGIIA) AP score variaton.

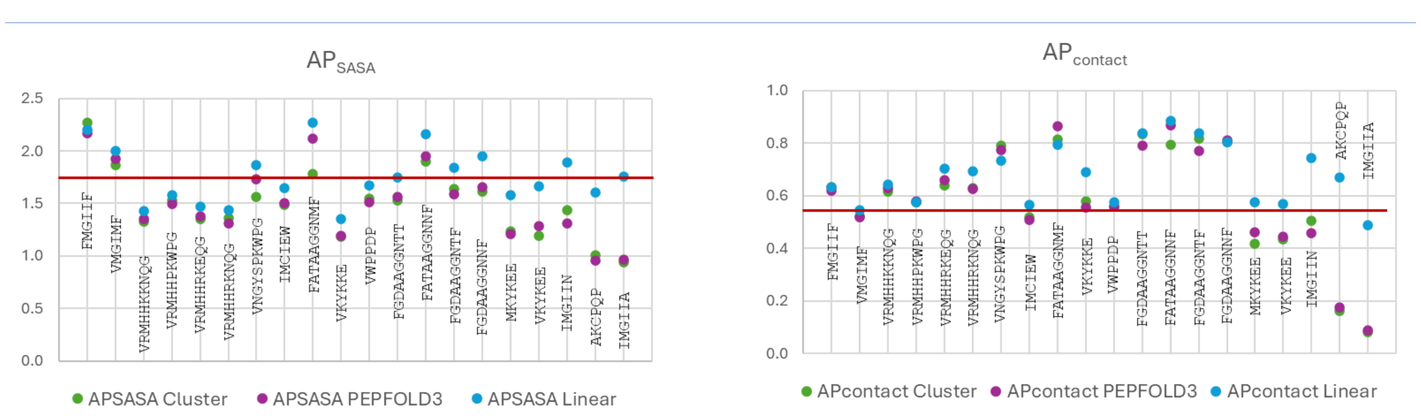

Figure 4 – The comparison of AP scores across 20 peptides. The red line represents the threshold above which peptides are considered as prone to aggregation. Its visible that cluster and PEPFOLD3 inputs are closely grouped while the linear molecule with the set secondary structure flag as an extended beta sheet shows deviation from the results.

Conclusions:

Secondary structure flags defined in the all-atom to CG conversion change the behavior of peptides in molecular dynamics simulations while structural factors and dihedral angles have minimal impact on the overall aggregation in large peptide systems.

HrZZ Croatian Science Foundation
DOK-2021-02-3496
UIP-2019-04-7999

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