Protein-Protein Association Reaction Study on GB1 Protein Dimerization in a Crowded Environment

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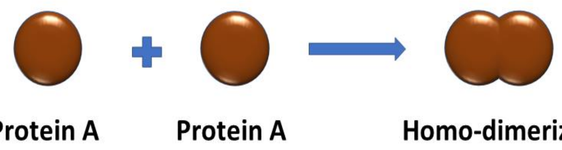
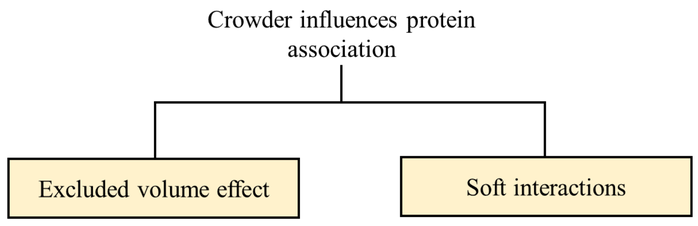
Abstract

Protein associated states are crucial in regulating functions such as DNA binding, immune response, enzymatic reactions, signal transduction. Recent studies indicate that the macromolecular crowders, that occupy 30-40% of the intracellular environment, can significantly favor the formation of protein self-aggregated complexes, whereas some crowders even impart a destabilizing effect on protein-protein complexes. In this work, we investigate dimerization of Immunoglobulin-binding protein G of the B1 domain of the Streptococcus species in presence of lysozyme crowders using Martini coarse-grained model. Simulations are biased with metadynamics and parallel tempering methods to ensure convergence of the free energy of binding. Our analysis shows that dimer formation is destabilized in presence of lysozyme crowders and the domain-swapped dimer of GB1 protein is more likely to be formed in both with and without crowder systems. The findings are compared with available experimental results and the scaled particle theory model.

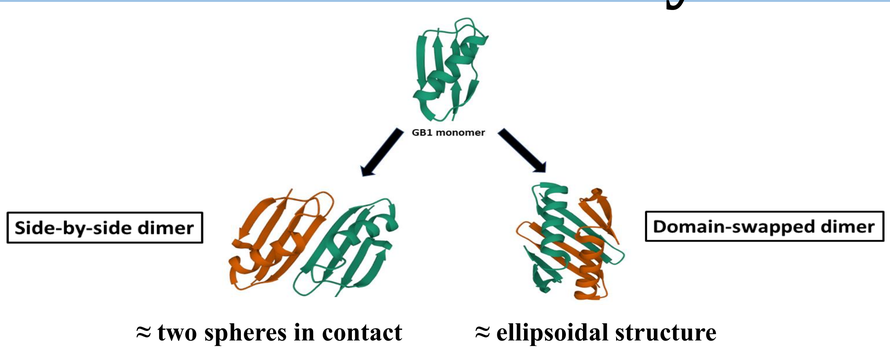
Introduction



- Dimeric proteins are found to regulate proteins in ion channels, enzymes, signal transduction, DNA binding, immune responses.
- Even unwanted self-aggregation of proteins can result in pathogenic structures such as amyloid-beta aggregation causing Alzheimer's disease.
- In crowded cellular environment,



GB1 as the model system

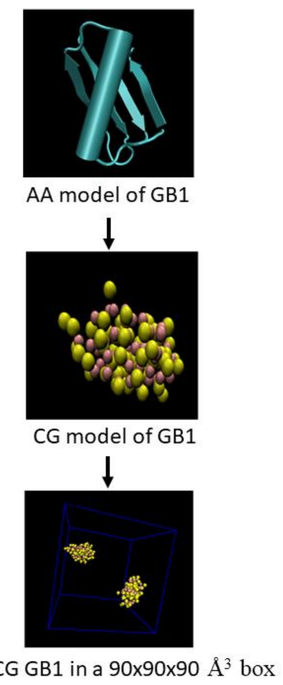


- Dimer formation requires specific contacts between two monomers.

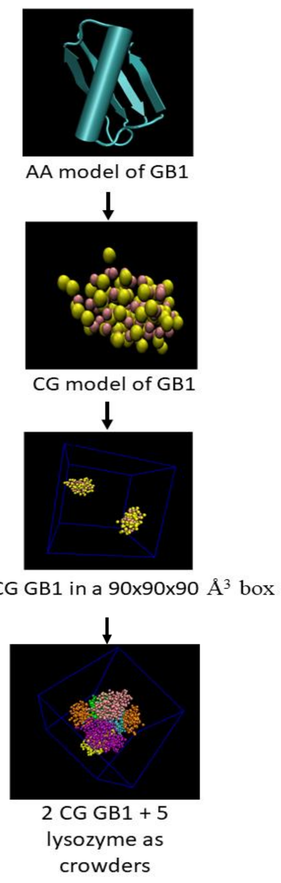
Methodology

❖ System preparation

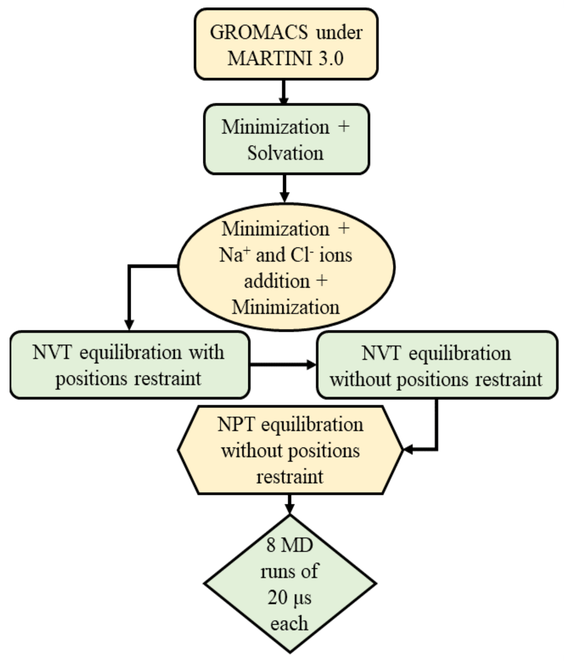
- Without crowders



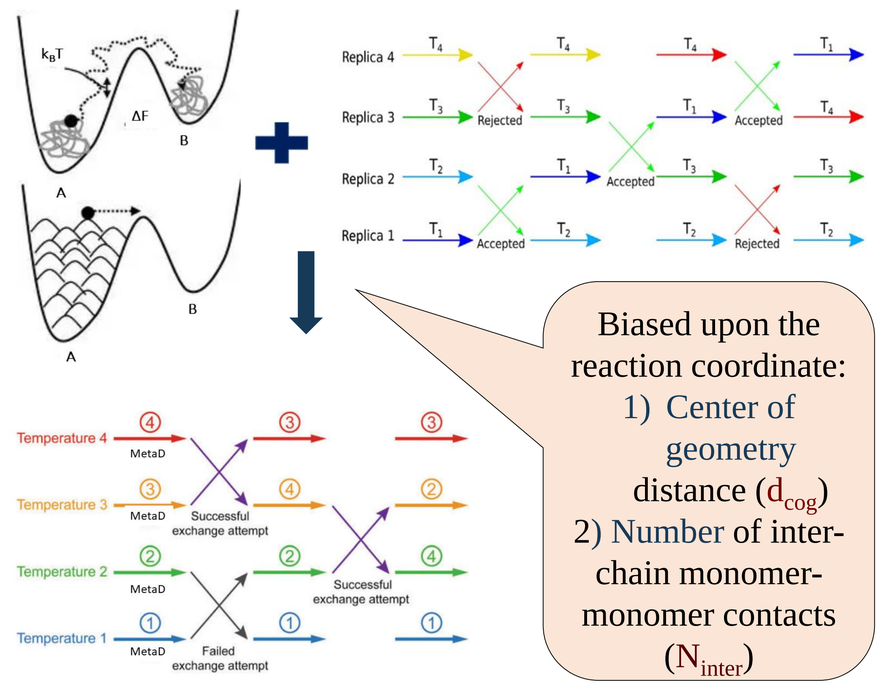
- With crowders



❖ Coarse-grained molecular dynamics simulations



❖ Parallel tempering metadynamics simulation



Results

- Free energy convergence of the system

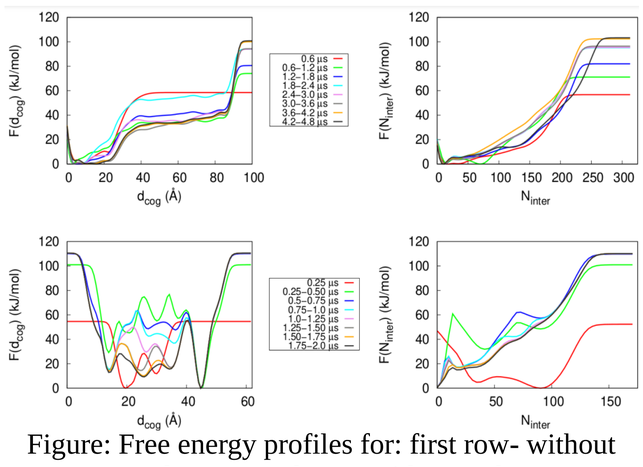


Figure: Free energy profiles for: first row- without crowders, second row- with crowders.

- Contact-maps of GB1 dimers formed

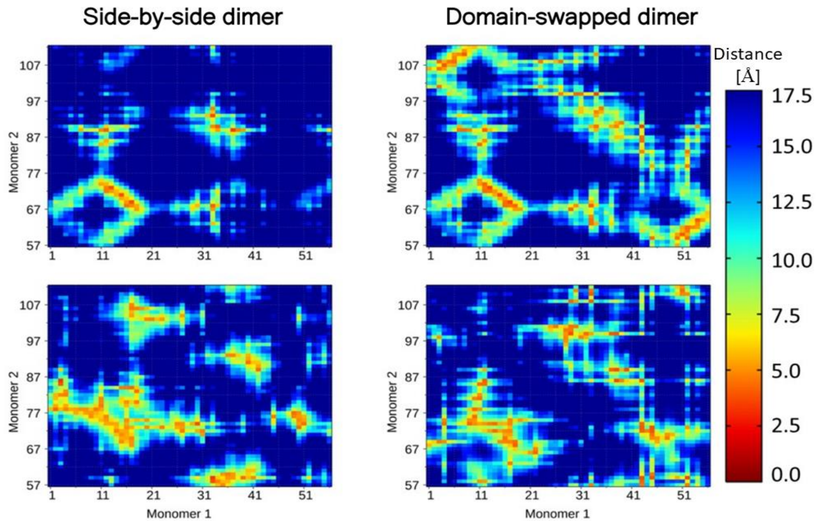


Figure: Barplot for the percentage of the probability to form side-by-side dimer and domain-swapped dimer within the selected d_{RMSD} range- 6 to 10 Å, 6 to 11 Å and 6 to 12 Å.

Methods	Side-by-side dimer	Domain-swapped dimer
Experiment[1]	**0.76**	**0.50**
SPT[1]	**-0.21**	**-0.38**
Martini model	**32.29**	

Table: Comparison of change in free energy change for dimerization in kJ/mol.

Conclusion

From the above results, we infer that:

- ✓ Out of the two dimers of GB1 protein, the side-by-side dimer and domain-swapped dimer, the domain-swapped dimer is more likely to be formed.
- ✓ Presence of lysozyme as the crowding agent, imparts a destabilizing effect on the homo-dimerization of GB1 protein.
- ✓ Soft attractive interactions between protein and crowders plays here a dominant role.

References

[1] A. J. Guseman, G. M. P. Goncalves, S. L. Speer, G. B. Young, and G. J. Pielak. Proc. Natl. Acad. Sci. USA 115, 10965 (2018).
[2] A. Barducci, M. Bonomi, M. K. Prakash, and M. Parrinello, Proc. Natl. Acad. Sci. USA 110, E4708 (2013).