BMC Bioinformatics

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Poster presentation

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Modeling mis-folded lysozyme aggregates

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from UT-ORNL-KBRIN Bioinformatics Summit 2008
Cadiz, KY, USA. 28–30 March 2008

Published: 8 July 2008

BMC Bioinformatics 2008, **9**(Suppl 7):P23 doi:10.1186/1471-2105-9-S7-P23

This abstract is available from: http://www.biomedcentral.com/1471-2105/9/S7/P23

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Background

Lysozyme is a 147 amino acid protein that can damage bacterial cell walls by destroying the glycosidic bond on the peptidoglycans molecule, particularly in gram-positive bacteria. Its native structure is composed of α and β domains and is cross-linked by four disulfides (Figure 1). Lysozyme can be aggregated by mutation of the lysozyme DNA sequence itself, or from the harsh environment of the cell inside (Figure 2).

Rosetta++ is freely distributed software used to predict all possible protein conformations by calculating the folding energy of the protein sequences. An included docking function is used to simulate a protein binding as homo- and hetero-dimers or trimers structures. This program is used to explore the possible conformations of one protein, which may not be easily found in the traditional approaches, such as NMR and crystallography. From these computer models, we can predict denatured and aggregate forms of proteins.

Materials and methods

1) Import native lysozyme sequence (gi:45384212) from NCBI and structure (PDB 1E8L) from PDB websites

2) Run lysozyme in *Ab initio* mode to start folding independently from the original protein sequence.

3) Docking each fold as homodimers to define the lowest energy to form lysozyme fibril structures.

4) Analyze the results.

Results

We generated 1,000 *Ab Initio* structures, at a denaturing temperature, from the original lysozyme sequence and let each structure dock together as homodimers for 10,000 structures. We generated 10 million structures and calculated the RMSD value when compared with the native structure. Previous evidence suggests the diameter of the lysozyme fibril structure is around 20 to 30 nm. Homodimers with radius of gyration less than 20 nm were considered. 422,983 of the 10 million homodimers structures were within the range 18 to 19.99 nm (Figure 3). The six lowest radii of gyration (18.01 nm to 18.04 nm) structures have a score range from -42.48 to -40.61 and RMSD of 11.917 when compared to the native lysozyme structure (Figure 4). All six of the structures came from the single lysozyme *Ab Initio* fold (LLt515). In addition, the first six models with the lowest energy scores (-68.04 to -67.56) have radii of gyration range from 19.65 to 19.81 nm and RMSD from 12.757 to 16.261 (Figure 5). Five of these structures came from lysozyme *Ab Initio* fold code LLt687 and the other from LLt998.

Conclusions and discussions

Most of lowest radius of gyration come from the same *Ab Initio* fold (Figure 4b), but all the six lowest energy scores have many different and diverse form of structures (Figure 5b). Therefore, if we want to group or cluster all this potential fibril homodimers, we should sort by radius of gyration to maintain the structure within groups.

For future study, we hope that the model of the fibrilar forms of denatured lysozyme will help us understand how to block fibril formation and model interactions with heat shock proteins or other chaperones during the dis-aggregation process (refolding mechanism) [2].

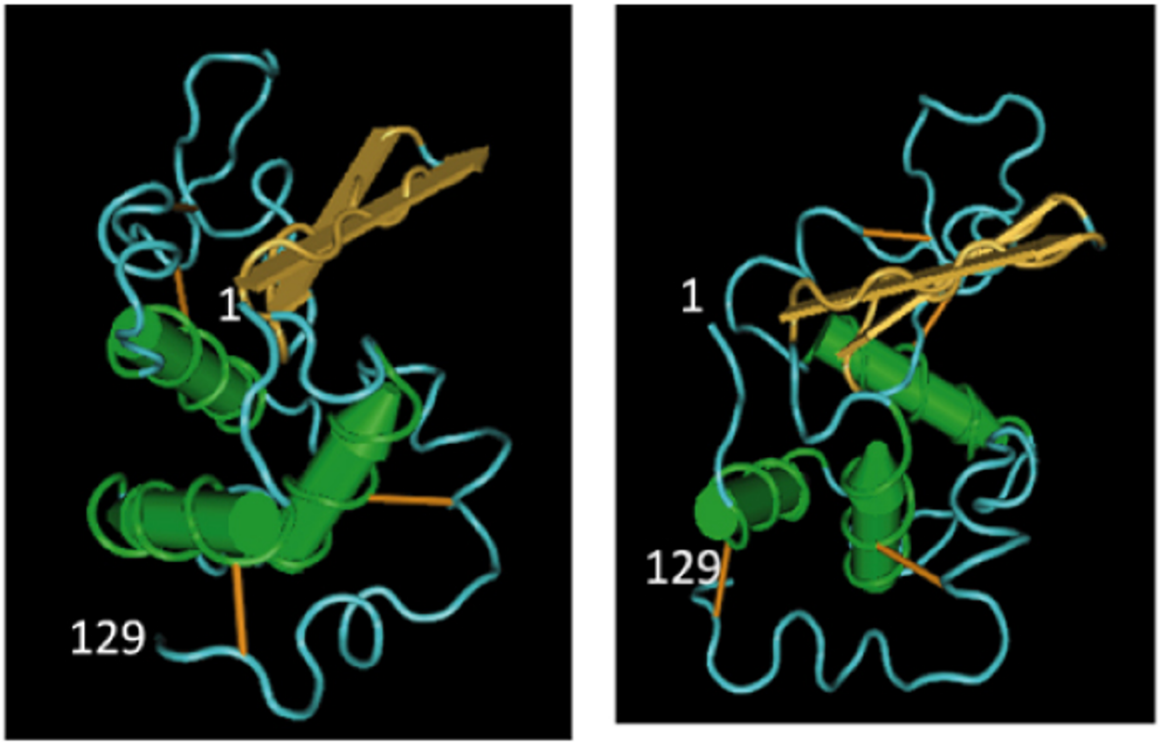

Figure 1
Native structure of white hen egg lysozyme (MMDB: 14790 PDB: pdb1E8L1E8L). The amino acid residues are numbered from the terminal α group (N) to the terminal carboxyl group (C). Orange lines indicate the four disulfide bridges. Alpha-helices are visible in the ranges 25 to 35, 90 to 100, and 120 to 125.

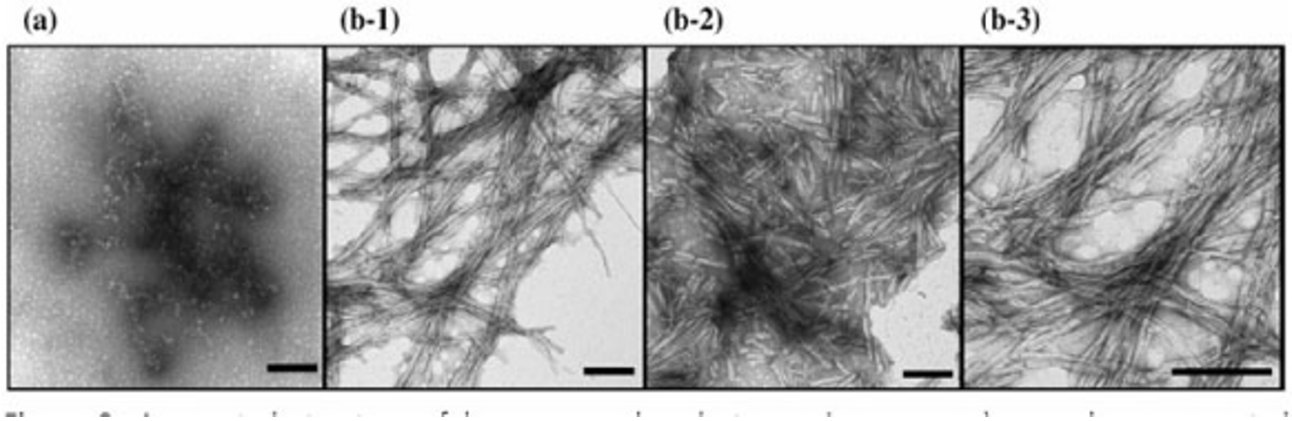

Figure 2
Aggregated structure of lysozyme under electron microscope. a) Random aggregated structures; b) fibril aggregated structures whose diameter is around 20 to 30 nm [1].

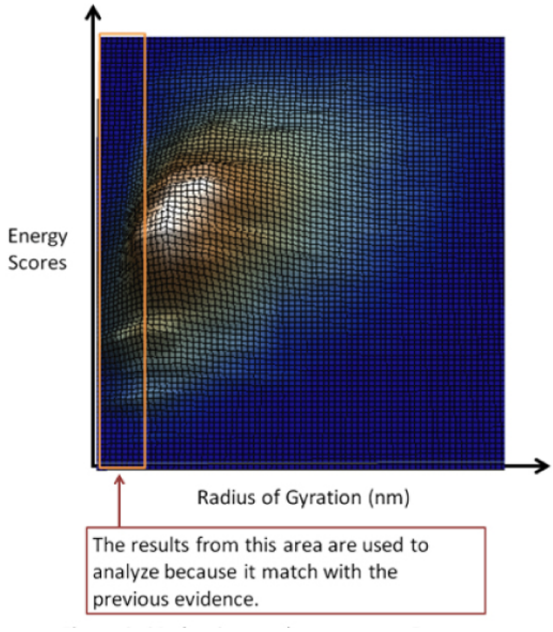

Figure 3
3D density graph represents energy score and radius of gyration for all 10 million homodimer structures. The orange box represents the area of the graph cutoff from 18 to 20 nm.

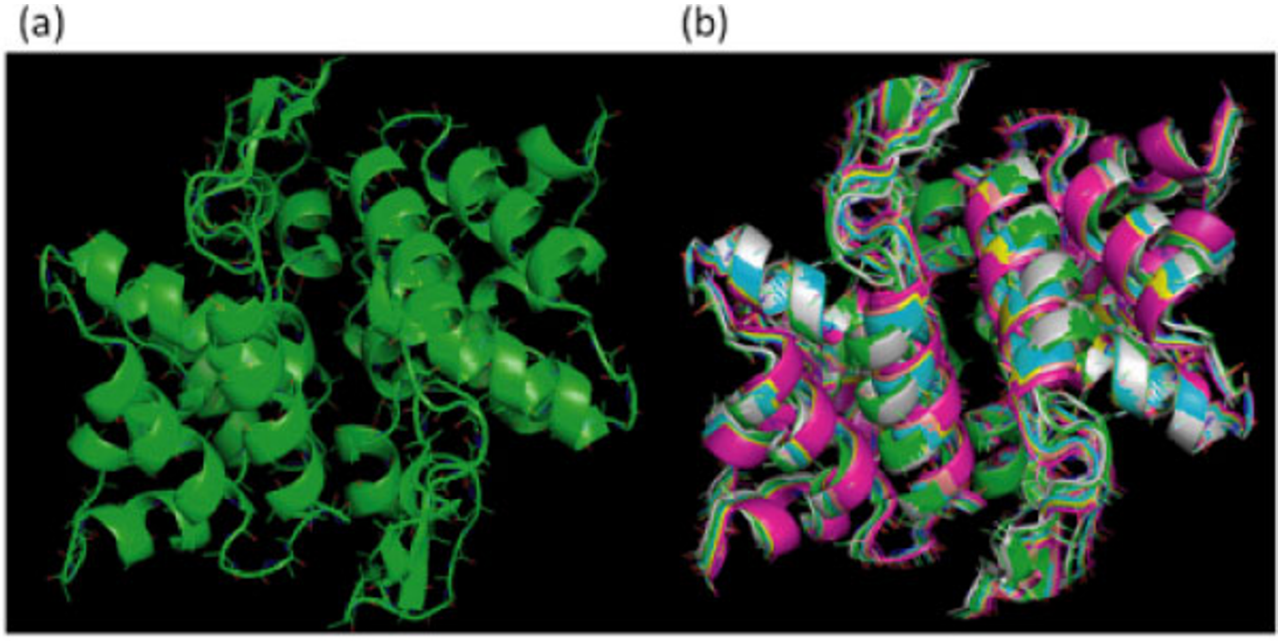

Figure 4
a) 3D structure of the lowest radius of gyration of lysozyme homodimers structures; (b) super-imposed 3D structure of six lowest radii of gyration lysozyme homodimer structures.

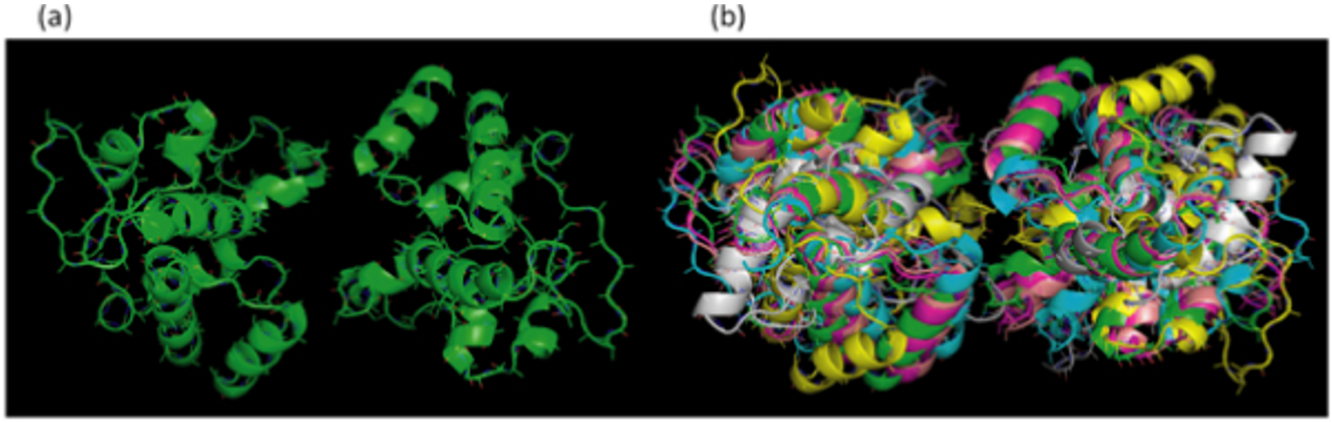

Figure 5
(a) 3D structure of the lowest homodimer structure. (b) Super imposed 3D structure of the six lowest scores of lysozyme homodimer structures.

Acknowledgements
We would like to acknowledge use of the BISC (Bioinformatics and Information Science Center) and Biotechnology Center of Western Kentucky University.

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