Molecular Dynamics Simulations of a Ten-Amino Acid Protein

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Introduction

Mini-proteins play an important role in the study of protein folding. The well-defined 3D structure and two-state folding along with their small size qualify mini-proteins as ideal to be studied using molecular dynamics simulations. In this study we simulate the folding of CLN025, a synthetic molecule with the sequence YYDPETGTWY that forms a beta hairpin as determined by X-ray crystallography and NMR analyses[1]. With this work we aim to examine the agreement between the available experimentally produced structures and the molecular dynamics structures and to validate the force fields used in the simulations through this comparison.

Methods

Molecular dynamics simulations were performed with the parallel molecular dynamics code, NAMD[2] and the use of three force fields of the Amber family: ff99sb-ildn, ff99sb-ildn-nmr, ff99sb*-ildn.

Results

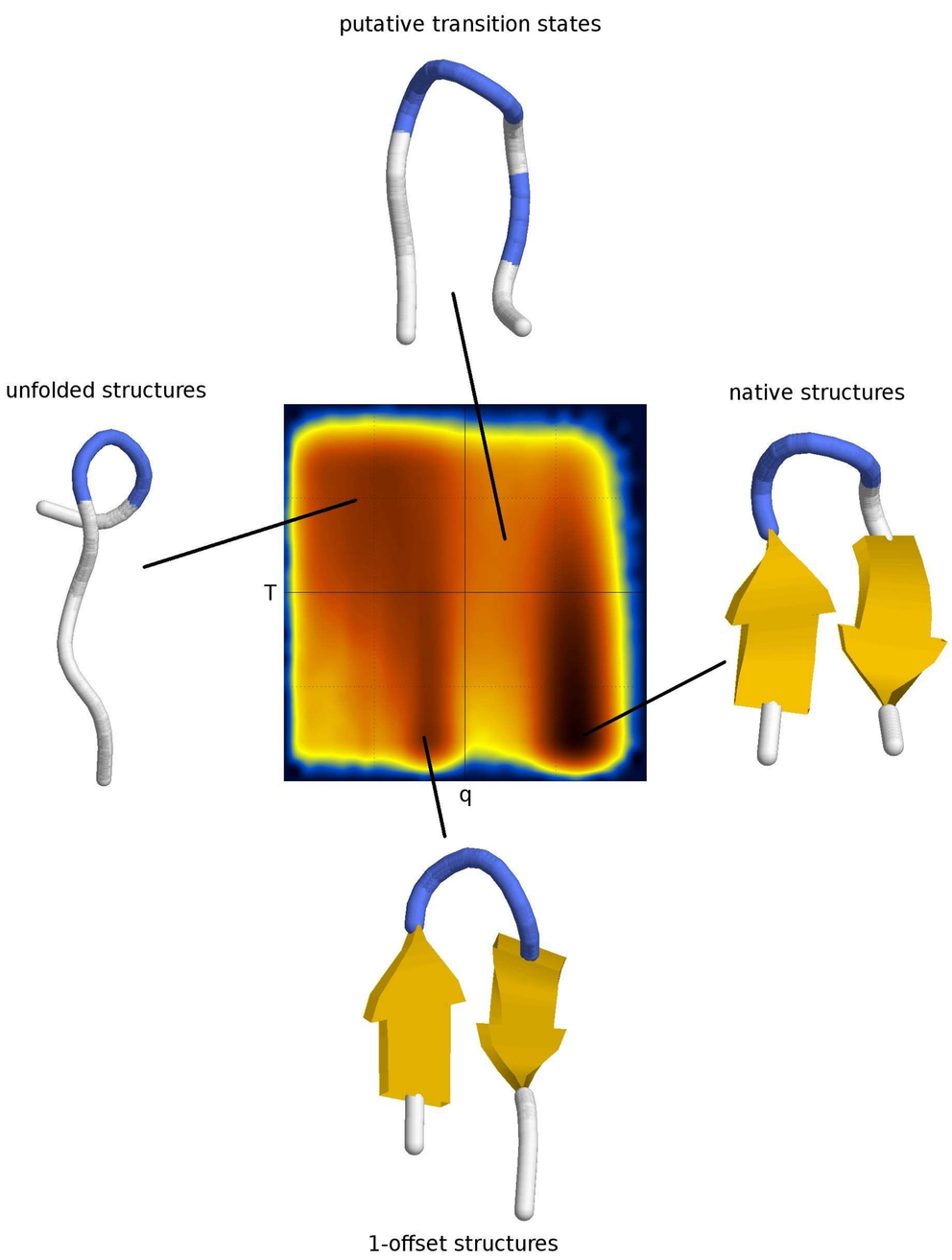

Figure 1: Amber ff99db*-ildn: Diagram presenting the similarity between the simulation and the experimental structure (q) in a temperature range of 280K to 530K (T). Characteristic structures are shown.

Figure 1 serves as an indicator of the general results produced by each simulation. The simulation repeatedly visits two certain stable structures, the native structure and a form of the beta hairpin with a one residue offset between the beta strands. The first cluster of conformations can be seen in the bottom right quadrant of the diagram and corresponds to high q values and low to medium temperature. The offset structures occupy a small area in the quadrant to the left and are characterized by medium similarity to the experimental NMR structure. The top left quadrant comprises solely of the unfolded structures that the simulation goes through. A noteworthy area is the one that lies between the 1-offset and native structures where putative transition states gather around a saddle point.

Figure 2 illuminates the subtle differences between the force fields. Based on this figure it appears that ff99sb*-ildn and ff99sb-ildn are the most similar among all pairs. However there's a clear distinction regarding the melting temperature for the native structure being lower in the case of ff99sb*-ildn.

Amber ff99sb-ildn-nmr is the force field that possesses the most differences from the other two. Firstly it contains far less 1-offset structures than ff99sb*-ildn and ff99sb-ildn, with ff99sb*-ildn being the one that includes the biggest cluster of 1-offset conformations. Another significant difference is that in the case of ff99sb*-ildn and ff99sb-ildn there's a region of high q values in the cluster of native structures that the ff99sb-ildn-nmr lacks.

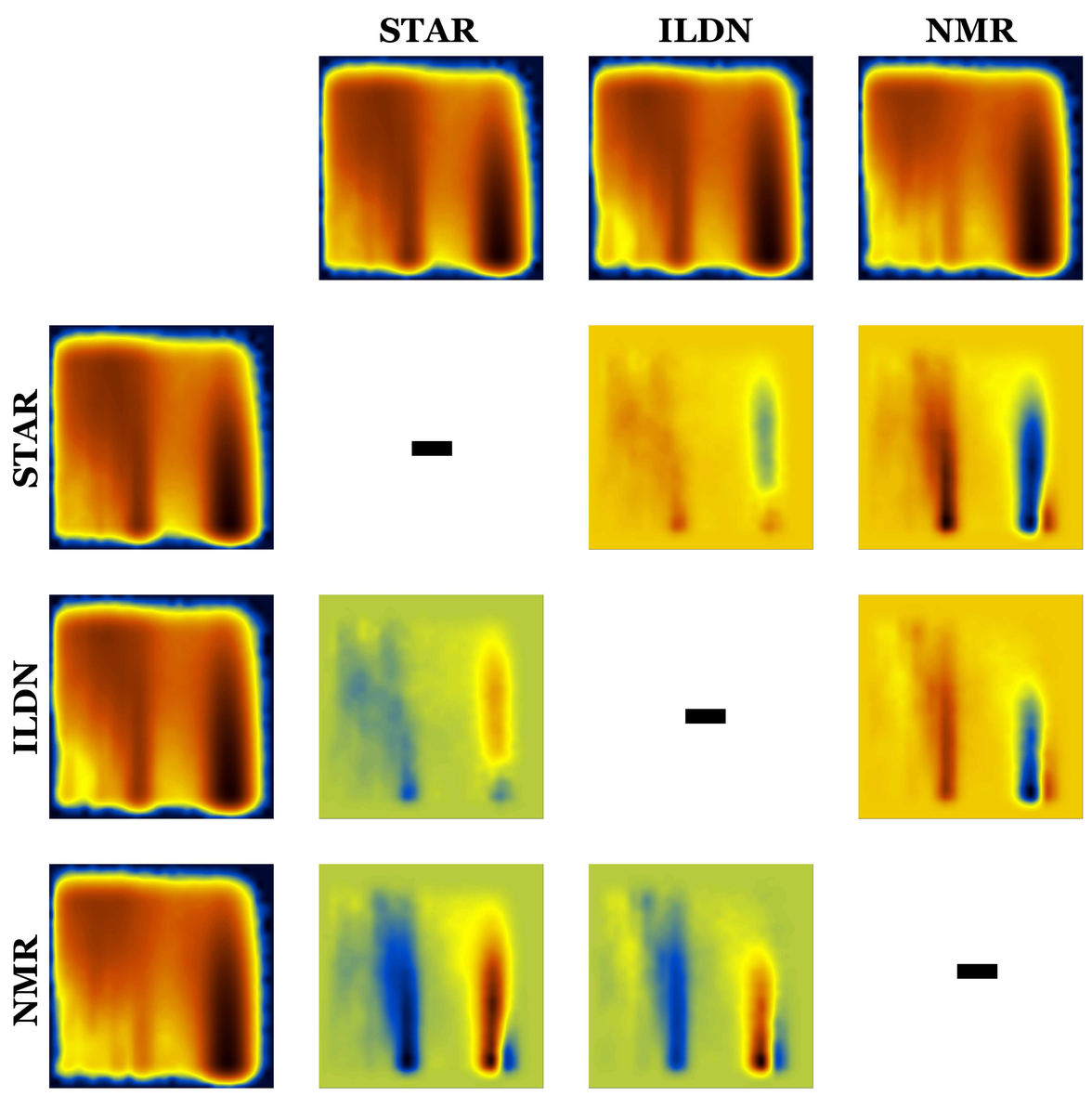

Figure 2: Table of force field comparison displaying the difference between each pair of force fields.

Conclusions & Future Work

To conclude, we have demonstrated that relatively minor changes in a force field can lead to significant changes in the predicted folding behavior of this well-studied peptide. The availability of extensive experimental data for this system should allow us to compare and validate the three force fields against the raw experimental (mainly NMR) data. Having said that -and based on the results shown in Fig.2- it appears that even at this early stage of the analysis the 99SB-STAR-ILDN variant possibly outperforms the other two variants, both with respect to the predicted thermodynamic stability of the folded state (less over-stabilization of the peptide's native state), and the agreement with the native-state structure (higher Q-values).

References

1. Shinya Honda et al., Crystal Structure of a Ten-Amino Acid Protein, J. Am. Chem. Soc., 2008, 130 (46), pp 15327–15331

2. James C. Phillips, Rosemary Braun, Wei Wang, James Gumbart, Emad Tajkhorshid, Elizabeth Villa, Christophe Chipot, Robert D. Skeel, Laxmikant Kale, and Klaus Schulten. Scalable molecular dynamics with NAMD. Journal of Computational Chemistry, 26:1781-1802, 2005