Folding simulations of a highly frustated peptide

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Motivation: Sanz and coworkers [1] showed that the choline binding region of the LytA protein (LytA197 – 210[wt])and its mutant LytA197 – 210[ND] are able to adopt a native-like structure in an aqueous solution and recognise choline. We have conducted folding molecular dynamics simulations of LytA197 – 210[ND] for a grant total of 13.7 μs using different combinations of parameters. During our simulations we reported only one folding event. In order to interpret this finding we run a series of calculations. Here, we present the results of our research.

Methods: All simulations were performed with the program NAMD[2] starting from the extended (unfolded) peptide state. The trajectories were analyzed using CARMA[3] and VMD [4]. Several different combinations of force fields (AMBER99SB and 99SB-ILDN), temperatures (320K, 340K, 360K) and water models (TIP3P, TIP4P-Ew) have been tested. For the purposes of this preliminary analysis, these trajectories have been treated as mergeable, and the results reported here correspond to a hypothetical trajectory that combines all of our simulations. Clearly, the resulting (merged) landscapes do not correspond to any physically valid description of an energy landscape, and can only be used for a coarse characterization of the peptide's behaviour.

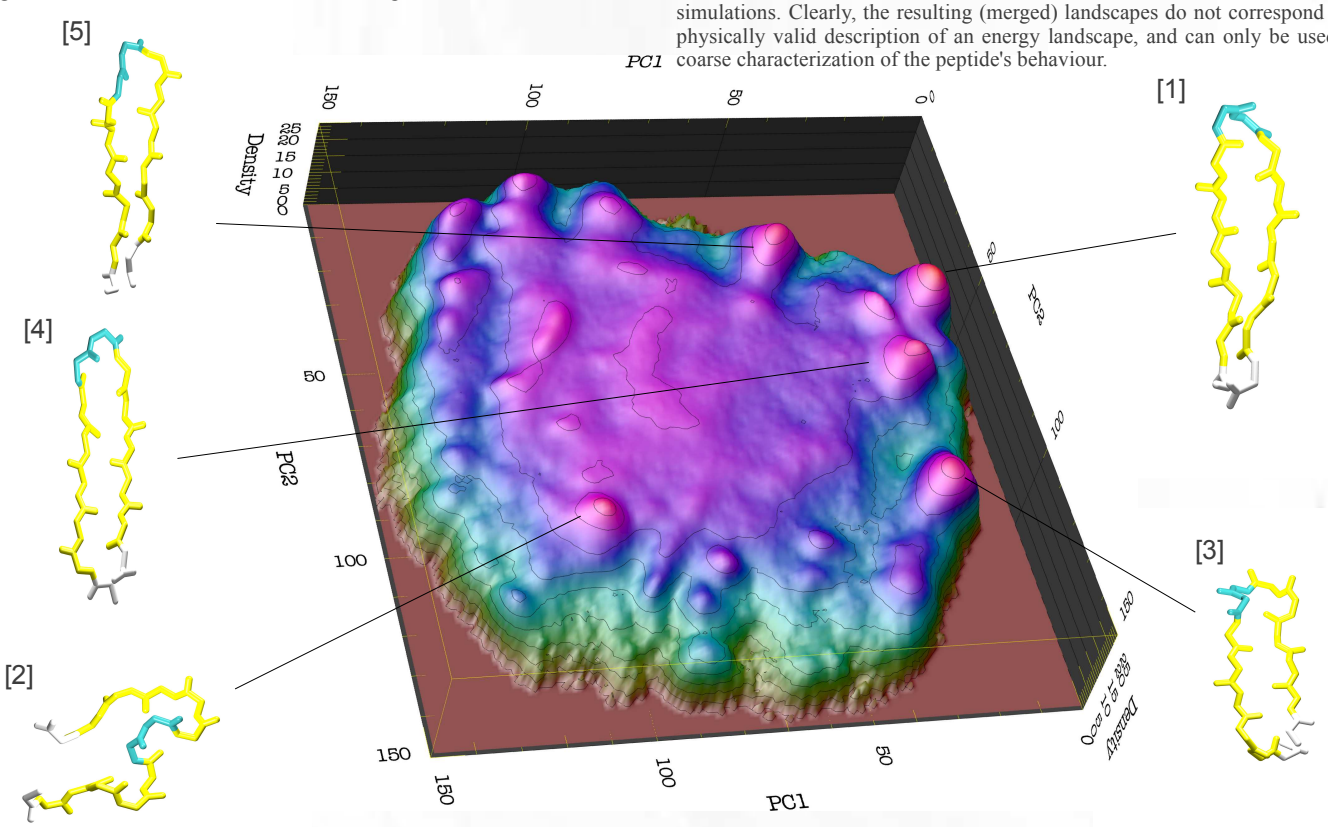

Fig.1 The central landscape depicts the distribution of the peptide's conformations projected on the top two principal components from dihedral principal component analysis performed with carma (image drawn with opendx). The cluster analysis has been performed using all 17 million peptide structures recorded in our simulations. Representative structures (backbone-only) of four of the major clusters are shown as skeletal models. DSSP-derived secondary structure assignments are indicated with color (cyan → turn, yellow → β, white → coil). The structure at the top-right-hand-corner is the native structure.

Results : Figures 1 & 2 show projections of our simulations on selected order parameters as indicated in the respective figure legends. Both diagrams appear to indicate the presence of significant frustration in the peptide's folding landscape. For example, the landscape of Figure 1 shows that numerous non-native conformations are sampled during the simulations, with no clearly identifiable funnel-like gradient leading to the native structure (noting in this connection that this diagram shows the distribution of no less than 17 million peptide structures). The few prominent conformations that are identifiable are comparable in density with the native conformation. We also note the presence of significant populations for β-hairpins with mis-aligned β-strands. Figure 2 resembles the energy landscapes for folding proteins[5,6] but lacks the pronounced curvature expected from a polypeptide that folds on an ideal funnel-like landscape. This is clearly seen by the accumulation of structures with both low Rg and low q values. The presence of a saddle point at q~0.5 may be indicative for the presence of a high-energy transition state leading to the native structure.

Discussion : In summary, and with the reservations arising from the limitations of our analysis, it appears that the LytA197-210[ND] peptide suffers from significant kinetic frustration with very many non-native structures being transiently stabilized during our simulations. The presence of a significant energy barrier at an assumed transition state (Figure 2) can not be excluded, but the absence of highly populated native-like intermediates indicates that there is no funnel-like gradient leading to native state.

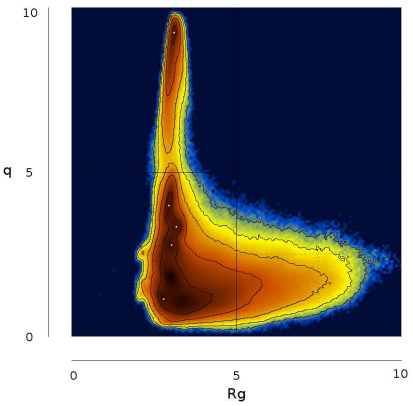

Fig.2 Folding landscape projected on the radius of gyration (Rg) vs. similarity with the native structure (q). The isolated peak at high q values correspond to the native structure. Note the presence of numerous structures with native-like radius of gyration, but low q values. The white dots represent the conformations 1, 4, 3, 5, 2, starting from the ones with the highest q values.

References

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