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Exploring the Free Energy Surface of Short Peptides by Using Metadynamics

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The free energy surface (FES) of three Poly-Alanine peptides is exhaustively reconstructed by using metadynamics. A specific collective coordinate has been introduced to account for the hydration of the N-terminal region of alpha-helical conformations. Calculations suggest that Poly-Alanine peptides mainly populate unfolded states. Interestingly FESs exhibit different properties among peptides thereby providing some hints on factors determining the conformational preferences of short Poly-Alanine sequences. Overall the calculations evidence the efficiency of Metadynamics in exploring free energy surfaces of biological relevant molecules.

1 Introduction

Biological macromolecules have typically access to a wide spectrum of conformations. Such a dynamical behavior, essential for solving the biological functions, is connected to a complex free energy surface (FES). With the growing power of calculators and the continuous refinement of force fields, molecular simulations have been increasingly employed to address for relevant biological topics. In this scenario, a demand for innovative tools allowing for an efficient exploration of the FES has pushed for the development of a variety of novel methods. Herein, to reconstruct the FES of polypeptides, we employ a method - Metadynamics - recently introduced by Parrinello and coworkers¹ and successfully applied to a large variety of scientific problems from physics to chemistry and biology. As test case, the FESs of small Poly-Alanine peptides are sampled.

2 Methods

Metadynamics performs an efficient exploration of multidimensional FES by means of collective coordinates (CVs) and a history dependent potential (eq.1):

$$F_G(s, t) = \int_0^t dt' W \exp\left(-\frac{s - s(x(t'))^2}{2\delta^2}\right) \quad (1)$$

The dynamics in the space of the CVs is guided by the free energy of the system plus the history-dependent potential which sums Gaussians of width d and weight W centered along the CVs trajectory up to time t (for further details see¹). Herein, we employed three different CVs. The first is the gyration radius calculated on the C-alpha atoms of the peptide. The second is the root mean square deviations of the dihedral angles compared to an

ideal alpha-helix. Finally, to account for the conformational stability of helical conformations, we biased the hydrogen bonds that the 4 N-terminal residues make with water (see discussion). The latter CV is accounted with the following formula:

$$\sum_{i=1}^4 \sum_{j=1}^{nr.Waters} \frac{1 - \left(\frac{r_i - r_j}{d_0}\right)^6}{1 - \left(\frac{r_i - r_j}{d_0}\right)^{12}} \quad (2)$$

with $d_0 = 0.22$ nm and the i running on the amide hydrogen atoms of the first four residues of the peptide (representing the N-terminal loop of an ideal alpha-helix) and the j running on all the acceptor oxygen atoms of the solvent. We simulated three poly-Alanine peptides of length 9, 14 and 19 (PolyA₉, PolyA₁₄ and PolyA₁₉, respectively). The simulations have been performed by using GROMETA^{2,3}, which is a metadynamics module developed to run in association with GROMACS, and GROMOS 53A6 forcefield. The system has been accommodated in a dodecahedron box with periodic boundary conditions. The box has been filled with SPCE water molecules. Peptide N- and C- terminal moieties have been modeled as uncharged. Non-bounded interactions have been treated by using a cutoff for Van der Waals (1.4nm) and PME for long-range electrostatic interactions (mesh spacing 0.125 nm). The dynamics have been simulated in the canonical ensemble, coupled with a Nose-Hoover thermal bath. The equilibration procedure has been performed as in Ref. 2. For each peptide, simulations have been carried out for 60ns starting by an ideal alpha-helical conformation.

3 Results and Discussion

We performed exhaustive metadynamics runs of PolyA₉, PolyA₁₄ and PolyA₁₉ with particular focus on the N-terminal hydration, for which a specific CV has been written. Indeed, the latter is known to be one of the possible strategies that nature adopts to stabilize alpha-helices⁴. To improve the sampling convergence in meaningful regions of the FES, the weight W has been rescaled according to the Well-Tempered dynamics¹. This allowed us to monitor convergence of the samplings. The 3D FES of PolyA₉ (Fig. 1) evidence that this peptide is unable to sample alpha-helical conformations. Indeed the peptide essentially populates unfolded states featured by a large distribution of gyration radiuses. The sampling evidences a minimally populated beta-hairpin state and an ensemble of kinked states, mainly featured by a central Hbond promoting a beta-turn. This result is in a good agreement with a recent NMR study⁵. On the other hand, the larger PolyA₁₄ (Fig. 2) and PolyA₁₉ (not shown) are able to marginally explore alpha helical regions. Notably, by passing from 9 to 14 and 19 Alanine residues, the distribution of gyration radiuses is dramatically affected with longer chains showing preference for collapsed structures (see 1D projections on CV2 in Fig. 1 and 2). It is very likely that the tendency to adopt more collapsed structures is a first step toward the formation of regular secondary elements as shown by the mild exploration of alpha-helix and a larger population of beta-hairpins. It is worth nothing that it was not possible to fully test the newly introduced N-terminal hydration CV since the simulated peptides are not properly able to populate the alpha helical structures. However, it is likely that for more helical peptides this CV would efficiently help the convergence of the Metadynamics sampling. Future development will focus on alpha-helical peptides for which a detailed thermodynamics and kinetics description is available in literature.

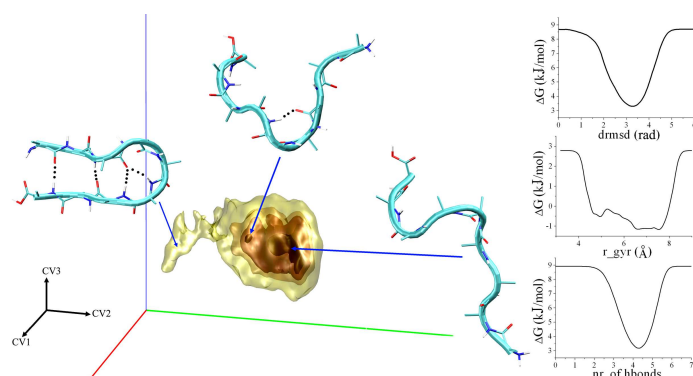


Figure 1. **FES of PolyA₉**. The left plot reports 3D FES (kJ/mol) with curves contoured at -10, -11, -11.8 and -12.4 kJ/mol. Blue arrows connect representative structures with respective regions of FES. Right panel reports FES projected on CV1 (top), CV2 (middle) and CV3 (bottom).

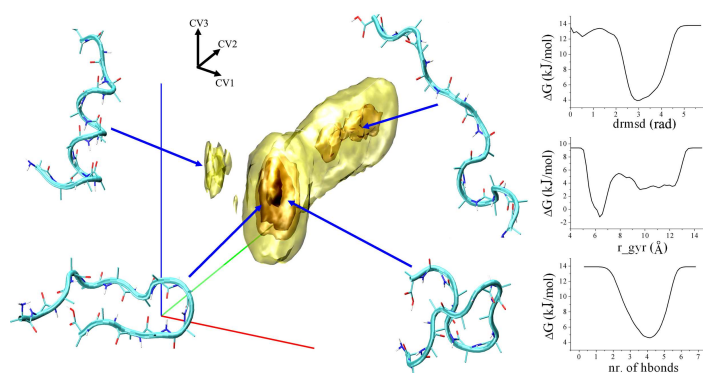


Figure 2. **FES of PolyA₁₄**. The plot is structured as in figure 1. Contour curves of the 3D FES are plotted at -7, -14, -16 and -18 kJ/mol.

Acknowledgments

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