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Prediction of Twist of Amyloid Fibrils Using Molecular Dynamics

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Many proteins and peptides form amyloid fibrils. These long, helically symmetric aggregates can be highly ordered but are not normally amenable to structure determination by X-ray crystallography or solution NMR. Therefore although amyloid fibrils of the same sequence can display substantial variation in gross morphological features such as twist (depending on seeding and on growth conditions such as pH) the atomic-level origins of this variation remain obscure. In order to probe the origins of the diversity in fibrillar twist we use the weighted-histogram analysis method of atomistic molecular dynamics (WHAM) to measure the free energy with respect to twist of two model polyalanine fibrils having different subunit-packing symmetries within the overall helical symmetry. We identify differences in twisting which arise from the differences in symmetry.

1 Introduction

The interest in amyloid formation arises from its involvement in a number of human diseases and from the potential of amyloid to serve as a nano-material if assembly could be sufficiently well controlled. A connection has been proposed between the free-energy of twisting of an amyloid sheet and the number of sheets which can be stacked together within a fibril[1], so a numerical method of calculating the free-energy of twisting is important for this reason as well as for the purpose of checking hypothetical atomic structures based on partial experimental data.

2 Materials and Methods

Two small model amyloid fibrils were chosen for this study, each composed of two β-sheets of six CH_3CO-$(Ala)_7$-$NHCH_3$ peptide strands. The model fibrils differed from each other in the symmetry of the arrangement of peptide strands: the first system (P) was composed of parallel β-sheets arranged face-to-face antiparallel to eachother (symmetry class 1 in the now-standard nomenclature[2]) and the second (AP) of antiparallel sheets arranged face-to-face (symmetry class 5).

Following previous studies of the free energy of DNA with respect to helical pitch[3], twist restraints were applied to adjacent peptide strands. Torsions were applied at 2nd, 4th and 6th C^α atoms of each strand in the pattern 2-4-4'-2' and 6'-4'-4-6, where prime (') indicates the C^α is on an axially adjacent strand within the sheet. WHAM[4] was applied, stepping in 2° increments from 0° to -16° and from 0° to $+16^\circ$, with a negative twist angle indicating left-handed helicity. Restraints had a strength of 750 $\mathrm{kcalmol}^{-1}\mathrm{rad}^{-2}$.

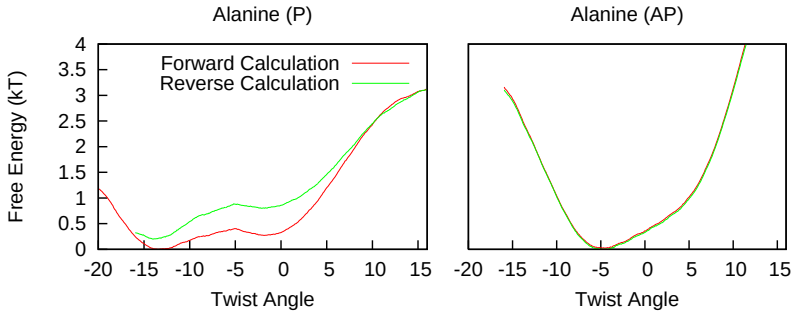

Figure 1. **Free energy with respect to twist.** Convergence is better for the AP system (reversibility is greater), and equilibrium twist is smaller. The P system shows a local minimum at a small twist, although the global minimum is strongly twisted. Energy is per torsion, shown are averages over the 12 central torsions.

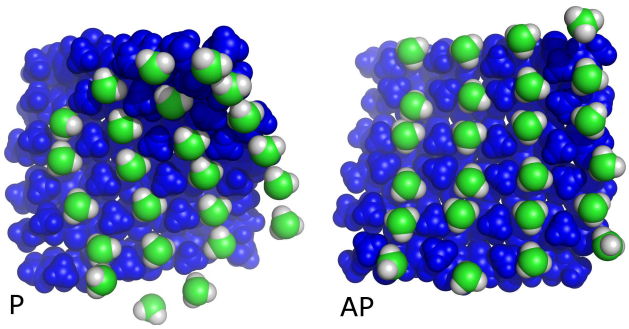

Figure 2. **Comparison of interfacial surfaces.** These snapshots of equilibrated unrestrained structures show the different characters of the two inter-sheet surfaces of the model fibrils. The back sheet is shown in blue, while only the inward-facing sidechains from the front sheet are shown (in green and white). The grooves in the AP surface are *compartmentalised*, preventing the sheets from sliding past eachother. This alters the twisting behaviour compared to the P system.

Measurements involving strands from either end of the fibril were discarded, in order to minimise contributions due to edge effects. Simulations were parameterised using the AMBER ff99-SB forcefield and run using the AMBER9[5] package, with a GBSA solvent model[6]. Unrestrained simulations were also run for 21ns, in order to verify the results. All simulations had additional distance restraints at the central hydrogen bond ladder to prevent them from dissociating, with a cuton of 5.5Å between the O and H atoms.

3 Results

Free energies with respect to twist are displayed for the P and AP systems in figure 1. By displaying results from both the forward (outward) and reverse (inward) simulations we can estimate the error in the calculation as the difference between them, which is modest for the P system and negligible for the AP system. Both systems twist; the P system twists more than the AP but also has a local minimum with less twist.

4 Concluding Remarks

Pioneering studies of β-sheet geometry[7] predicted a greater twist for antiparallel sheets. The tendency of our P systems to twist more than the AP systems therefore requires explanation. Assuming that both results are correct, the source of the difference must be the interface between the two sheets, as the original studies were of isolated sheets. Figure 2 shows that the sheet-sheet interface for AP amyloid is more complex than for P, having a knobs-and-holes character. This leads to a diminished flexibility away from the rectangular conformation, thus limiting twist.

The presence of a local minimum for the twist of the P system suggests that variation in twist of experimentally observed fibrils could arise not only from variation in packing symmetry but also potentially from kinetic trapping in states which have a twist other than that of the global minimum.

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