**Supplementary information for:**

# Energetics Underlying Twist Polymorphisms in Amyloid Fibrils

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**Detailed description of the potential of mean force calculation.**

Generally, perturbed potential energy function, $U(\mathbf{R}) = U_0(\mathbf{R}) + W(\mathbf{R})$, can be used to sample configurations, $\mathbf{R}$, difficult to access by equilibrium Molecular Dynamics (MD) simulations. Typically a series of umbrella simulations, *j*, supplemented by a perturbing potential, $W_j(\mathbf{R})$, are used to study a system along one or more reaction coordinates (functions of $\mathbf{R}$). The resulting biased distributions, $\rho_j^{(b)}(\mathbf{R})$, may be unbiased, $\rho_j^{(u)}(\mathbf{R}) = e^{\beta[W_j(\mathbf{R})-f_j]}\rho_j^{(b)}(\mathbf{R})$, and optimally combined with the weighted histogram analysis method (WHAM), $\rho_0(\mathbf{R}) = C\sum_{j=1}^{N} \frac{n_j}{\sum_{k=1}^{N} n_k e^{-\beta[W_k(\mathbf{R})-f_k]}} \rho_j^{(b)}(\mathbf{R})$. $\rho_0(\mathbf{R})$ can then be used to calculate ensemble average of arbitrary quantities as here the probability distributions in the $x_0$ and $x_1$ dimensions:

(1) $$\rho(x_0, x_1) = \int d\mathbf{R}\ \rho_0(\mathbf{R})\ \delta\left(x_0 - x_0'(\mathbf{R})\right)\ \delta\left(x_1 - x_1'(\mathbf{R})\right)$$

(2) and finally $$w(x_0, x_1) = -k_B T \ln\left[\rho_0(x_0, x_1)\right]$$

More details of our adaptation of the original works of Kumar[1,2] and Souailles and Roux[3] readers should refer to our previous work.[4]

Umbrella simulations were performed using the dihedral angles between consecutive peptides in a sheet (Figure 2) to control the overall twist of the cross-β structure. The biasing potential takes the form:

$$W_j(\mathbf{R}) = \tfrac{1}{2}\sum_{p=1}^{38} k_\theta\left(\theta_p(\mathbf{R}) - \theta_j^{(0)}\right)^2$$

where $\theta_p(\mathbf{R})$ are the 38 independent dihedrals; $\theta_j^{(0)}$ is the angle reference value in the $j^{\text{th}}$ umbrella trajectory, it is the same for all angles and goes from -20 to 20 degrees with 0.5 degrees increments resulting in 81 umbrella windows; $k_\theta$ was set to $10^4$ kJ mol$^{-1}$ rad$^{-2}$ (3.05 kJ mol$^{-1}$ deg$^{-2}$).

Each umbrella window was simulated for 5 ns, starting from a conformation of the cross-β structure close to the target value. The last 4 ns of each window were used in the PMF calculation. The error estimates of the final PMF were obtained through a bootstrap procedure in which each umbrella simulation was decomposed into four 1 ns windows. Hundred bootstrapping cycles were performed.

Once the PMF was resolved in the 38 dimensional dihedral space the probability distribution was projected onto a reduced two-dimensions space, $x_0$ and $x_1$. $x_0$ is the average dihedral angle of the 38 individual angles and $x_1$ is the root mean square deviation of the individual dihedrals from the average value of a conformation. The final PMF, $w(x_0)$, was obtained by integrating the 2D-PMF on the RMSD dimension from 0 to 1 degree.

(3) $$w(x_0)_{x_1<1} = -k_B T \int_0^1 dx_1 \ln\left[\rho(x_0, x_1)\right]$$

The range of RMSD used assures that we account only for the data present in the very close vicinity of the 38 dimensional diagonal in the dihedral space.

It is important to note that the full PMF calculated is not the complete 38D-PMF in the sense that for each angle the full range of values of the 37 other dimensions is not sampled. The reaction coordinate we use corresponds to a walk along the diagonal of the 38 dimensional dihedral space where all the dihedrals evolve simultaneously. In other words the cross-β structure twists homogeneously. Although it is difficult to quantify the deviation of this path from the full PMF the strong correlation between the angles upon twisting (data not shown) suggests it is small.

Note, when energetic and structural quantities are reported as a function of the twist angle it refers to the twist angle between two peptides and not the overall cross-β structure angle. Each quantity (energy or structural data) was thus associated with the 38 values of twist angle between peptide-pairs found in the cross-β structure for a given conformation. The twist angle/quantity pairs were accumulated over the course of the simulation and then averaged using bin of 0.2 degree for the twist angle. This is equivalent as using the average cross-β twist angle but allows to obtain continuous and smooth curves over the full range of angles explored.

References:


(1) Kumar, S.; Rosenberg, J. M.; Bouzida, D.; Swendsen, R. H.; Kollman, P. A. THE Weighted Histogram Analysis Method for Free□Energy Calculations on Biomolecules. I. the Method. *J. Comput. Chem.* **1992**, *13* (8), 1011–1021.

(2) Kumar, S.; Rosenberg, J. M.; Bouzida, D.; Swendsen, R. H.; Kollman, P. A. Multidimensional Free□Energy Calculations Using the Weighted Histogram Analysis Method. *J. Comput. Chem.* **1995**, *16* (11), 1339–1350.

(3) Souaille, M.; Roux, B. Extension to the Weighted Histogram Analysis Method: Combining Umbrella Sampling with Free Energy Calculations. *Computer Physics Communications* **2001**, *135* (1), 40–57.

(4) Periole, X.; Knepp, A. M.; Sakmar, T. P.; Marrink, S. J.; Huber, T. Structural Determinants of the Supramolecular Organization of G Protein-Coupled Receptors in Bilayers. *J. Am. Chem. Soc.* **2012**, *134* (26), 10959–10965.

(5) van Gunsteren, W. F.; Billeter, S. R.; Eising, A. A.; Hünenberger, P. H.; Krüger, P.; Mark, A. E.; Scott, W. R. P.; Tironi, I. G. *Biomolecular Simulation: the GROMOS96 Manual and User Guide*; vdf Hochschulverag 33 AG an der ETH, Zurich/Biomos BV, Groningen, 1996.

## Supplementary Figures

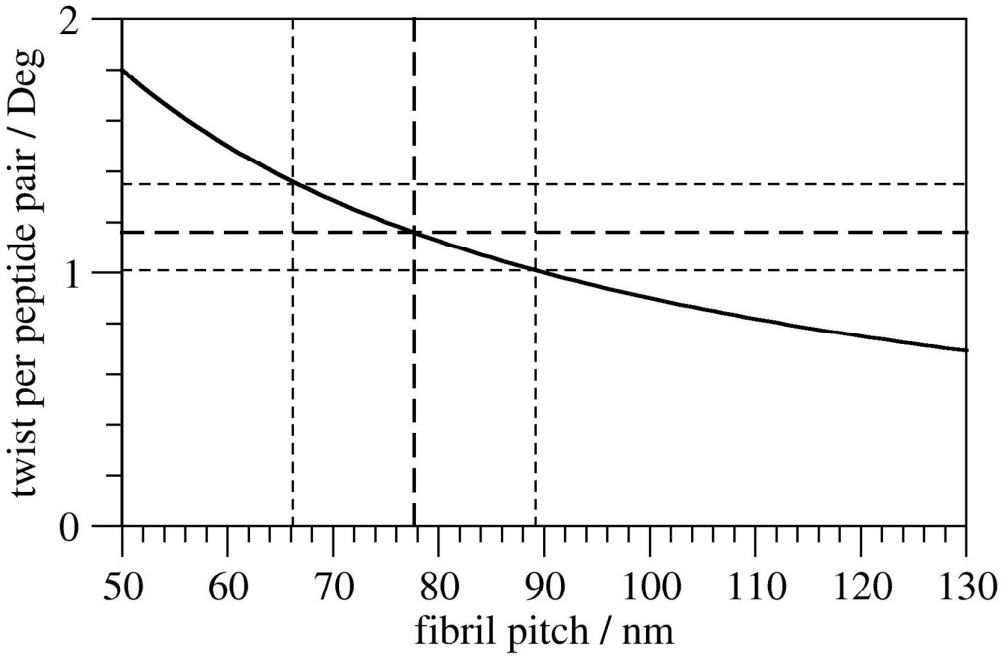


**Figure S1.** Relationship between the pitch and the twist per peptide of a generic fibril. It is assumed that the distance between strands in a β-sheet is 0.5 nm so the twist may be calculated using the expression: twist = 180 (deg) / [pitch (nm) / 0.5 (nm)]. 180 degrees represents the rotation of the fibril between two pitches.

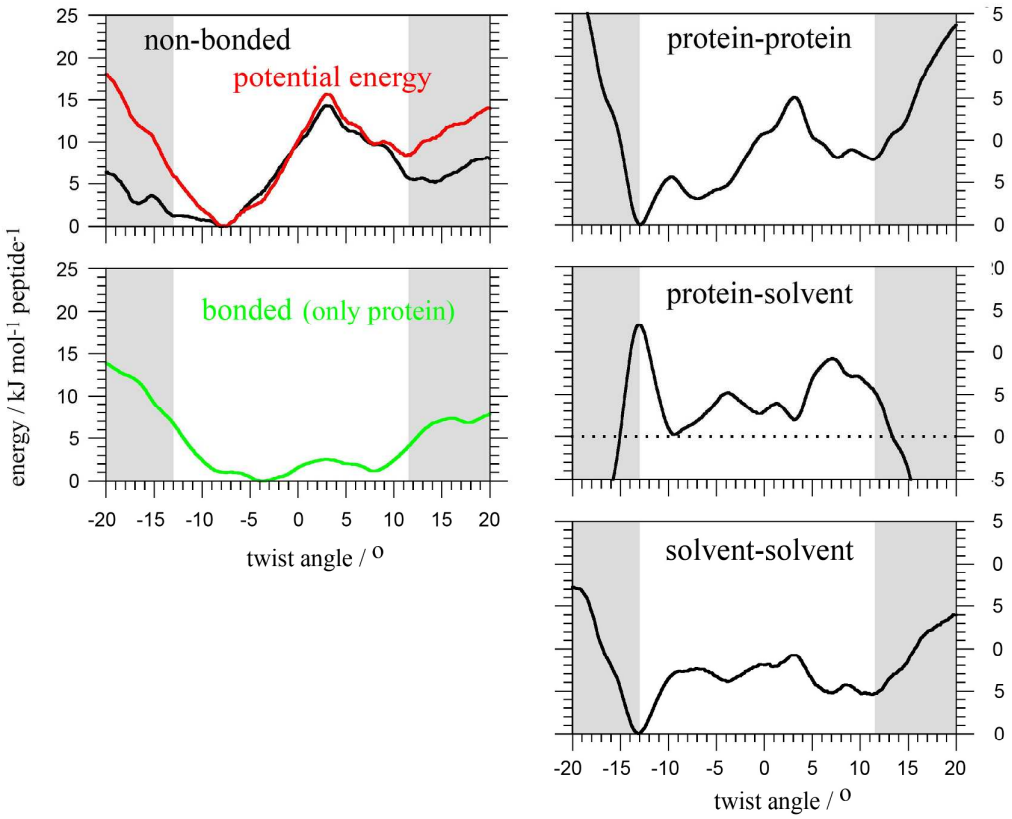


**Figure S2.** Decomposition of the potential energy (enthalpy) of the system (ΔH) into bonded and non-bonded terms and the protein and solvent contributions. ΔH= potential energy = bonded + non-bonded = protein-protein + protein-solvent + solvent-solvent + bonded. Non-bonded = protein-protein + protein-solvent + solvent-solvent. The geometry of the solvent molecules is restrained and therefore does not have a bonded contribution. The values were extracted from the force field G43a1 of the GROMOS series.[5] The right column is shown in the main text in Figure 6.

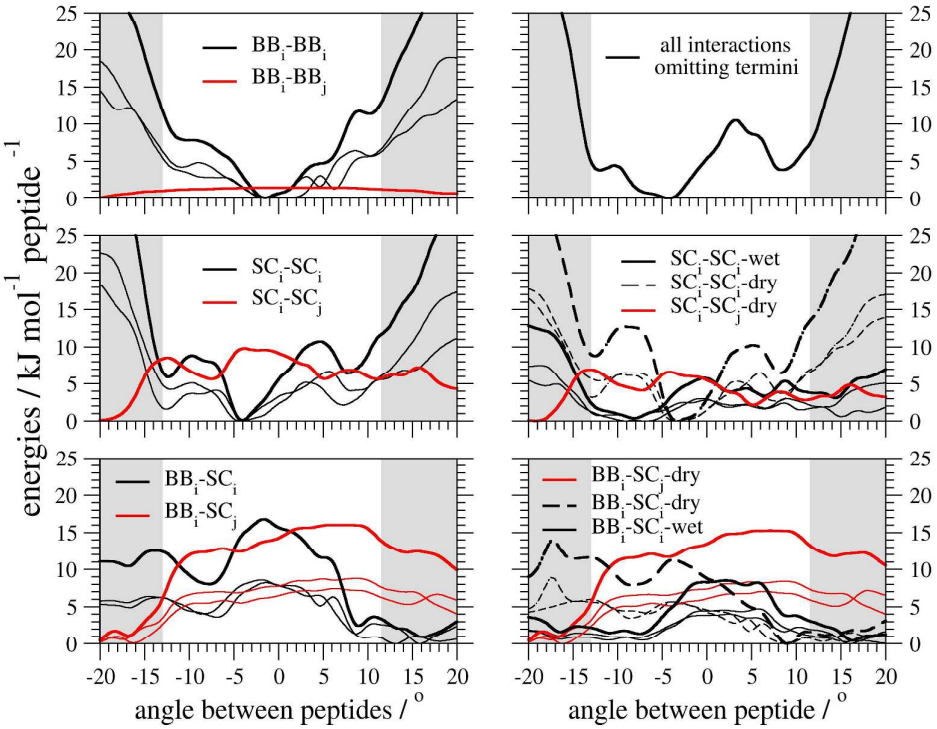


**Figure S3.** Further decomposition of the backbone (BB) and side chain (SC) contributions to the protein-protein non-bonded interactions as found in Figure 7 in the main manuscript. All interaction omitting termini = BB & SC in Figure 7 in the main manuscript. Indices i and j are used to differentiate the two sheets of the cross-β structure and therefore denote intra (i,i) and inter-sheet (i,j) interactions. Notations wet and dry denotes the interactions between the BB and SC occurring in the wet or dry interface of the cross-β structure (see main Figure 2) [ref]. The tick lines correspond to the energy associated to whole structures. The thin lines represent the individual sheets separately when appropriate, which gives an indication of the variability of the values.

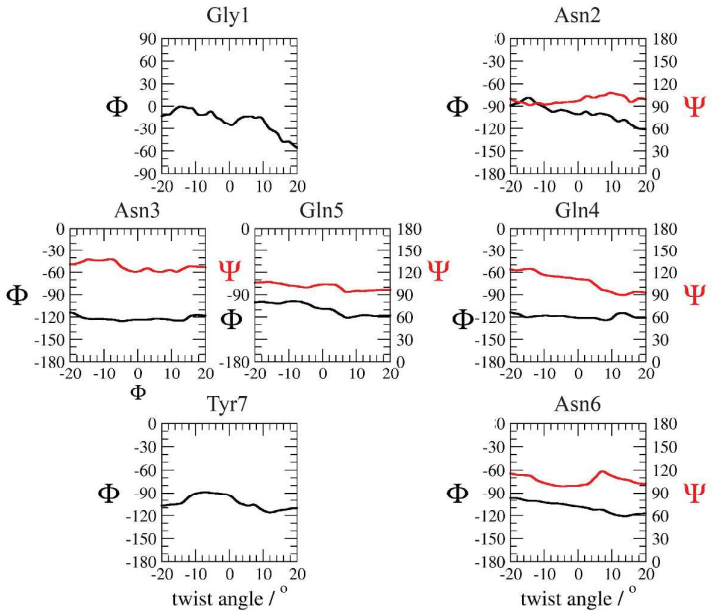


**Figure S4.** Evolution of the phi (black) and psi (red) angles of the peptide's backbone with the twist angle of the cross-β structure. The residues are ordered according to the interface their side chains contribute to. The left column shows the residues part of the wet interface (exposed to the aqueous phase) and the right column the residues part of the dry interface (facing the other protofilament).

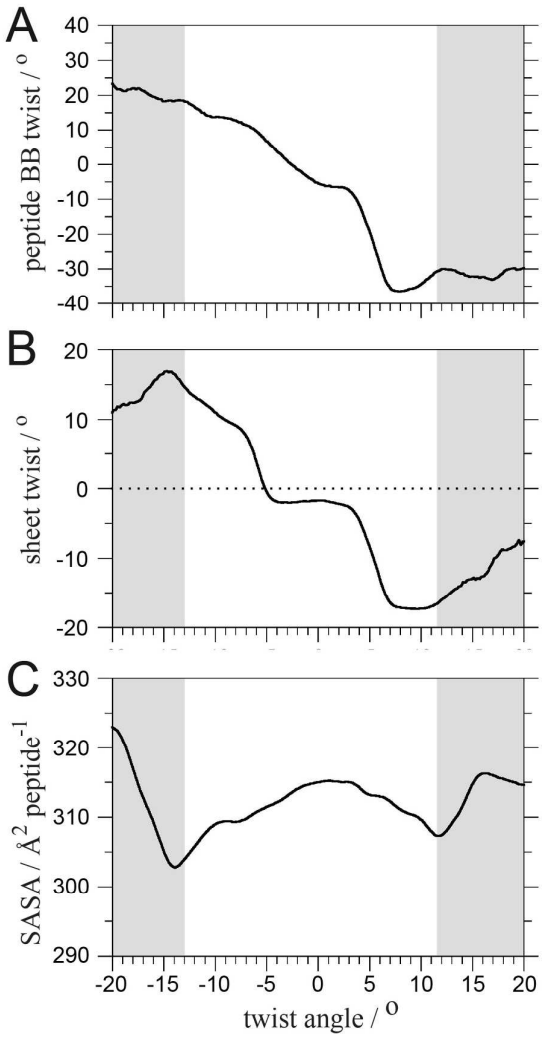


**Figure S5.** Properties of the cross-b structure as a function of its twist. A) Twist of the peptide's backbone (along each strand). The backbone's twist was reported by the angle between the C-O vectors of residues Asn2 and Asn6. B) Cross angle between the two facing sheets. It was measured as the angle between vectors aligning with the sheets. C) Solvent accessible surface area of the cross-β structure.