Supporting Information to "Atomistic Fibrillar Architectures of Polar Prion-inspired Heptapeptides"

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Contents

1 Equilibration protocol for molecular dynamics simulations

- Initial minimization 2000 points; 1000 with steepest descent method, then conjugated gradient;
- 200 ps of NVT dynamics rising the temperature from 0 to 100 K in the first half; there is a 2.0 (kcal/mol·Å^2) constraint on backbone atoms;
- 1 ns NPT dynamics rising the temperature from 100 to 150 K in the first quarter of the simulation and keeping it fixed to 150 in the rest; 1.0 (kcal/mol·Å^2) constraint on backbone atoms;
- 1 ns NPT dynamics at 150 K with no restraint;
- 1 ns NPT dynamics rising the temperature from 150 to 200 K in the first quarter of the simulation and keeping it fixed to 200 in the rest; 1.0 (kcal/mol·Å^2) constraint on backbone atoms;
- 1 ns NPT dynamics at 200 K with no restraint;
- 1 ns NPT dynamics rising the temperature from 200 to 250 K in the first quarter of the simulation and keeping it fixed to 250 in the rest; 1.0 (kcal/mol·Å^2) constraint on backbone atoms;
- 1 ns NPT dynamics at 250 K with no restraints;
- 1 ns NPT dynamics rising the temperature from 250 to 300 K in the first quarter of the simulation and keeping it fixed to 150 in the rest; 1.0 (kcal/mol·Å^2) constraint on backbone atoms;
- 1 ns NPT dynamics at 300 K with no restraints.

2 Structure of the NY7 peptide

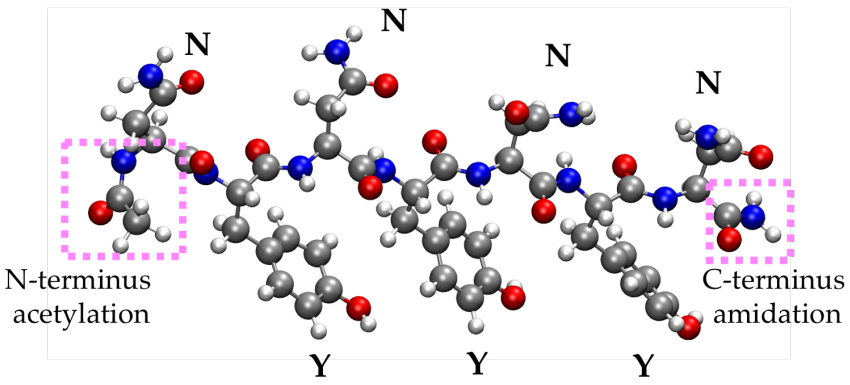


Figure S 1: Structure of the NY7 peptide with acetylated N-terminus and amidate C-terminus. The peptide has a β secondary structure that will be maintained in the fibrillar architecture.

This geometry of the initial strand is shared between all three heptapeptides, NY7, SY7 and GY7.

3 Definition of the twist angle

For each β-sheet, two vectors are defined considering strands 1 and 10 of each sheet. A vector is defined for each strand pointing from the N atom of the NHE amidated C-terminus to the carbonyl C atom of the acetylated N-terminus. The angle ϕ formed between the vectors of strands 1 and 10 has been computed along the trajectory. v_1 and v_3 are the vectors belonging to the first β-sheet and v_2 and v_4 those belonging to the second. The angle between v_1 and v_3 takes the name of ϕ_1 and the angle between v_2 and v_4 takes the name of ϕ_2.

4 Definition of the tilt angle

The tilt angle measures the planarity of the β-sheets along the molecular dynamics trajectory. it is the angle between the vectors defined between the twentieth and first frame and that bewtween the tenth and first frame, using as reference the α carbon of the central tyrosine residue of each strand.

5 Relative energies of the eleven steric zipper models

In this section we present the relative energies of the eleven possible steric zipper models for NY7, SY7 and GY7 along the 100 ns molecular dynamics trajectories. A Bezier smoothing has been applied to each dataset. Dashed lines indicate unstable models. i.e. models that lose the steric zipper organization along the trajectory.

5.1 Asparagine-Tyrosine systems - NY7

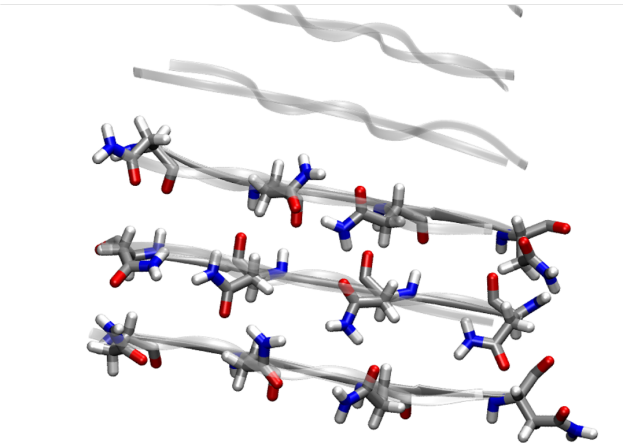


Figure S 2: Alignement of asparagine residues in the AP-FF2-UEQD architecture of NY7.

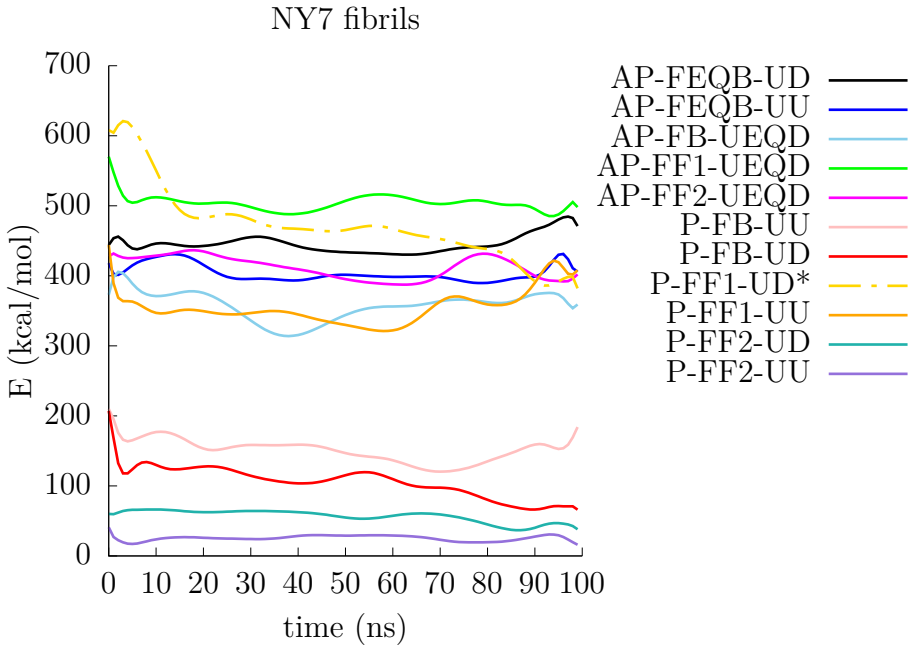


Figure S 3: Relative energies of NY7 fibril models.

The most stable architectures are P-FF2-UU and P-FF2-UD, in both cases asparagine residues are at the interface and tyrosines exposed to the solvent.

5.2 Serine-Tyrosine systems - SY7

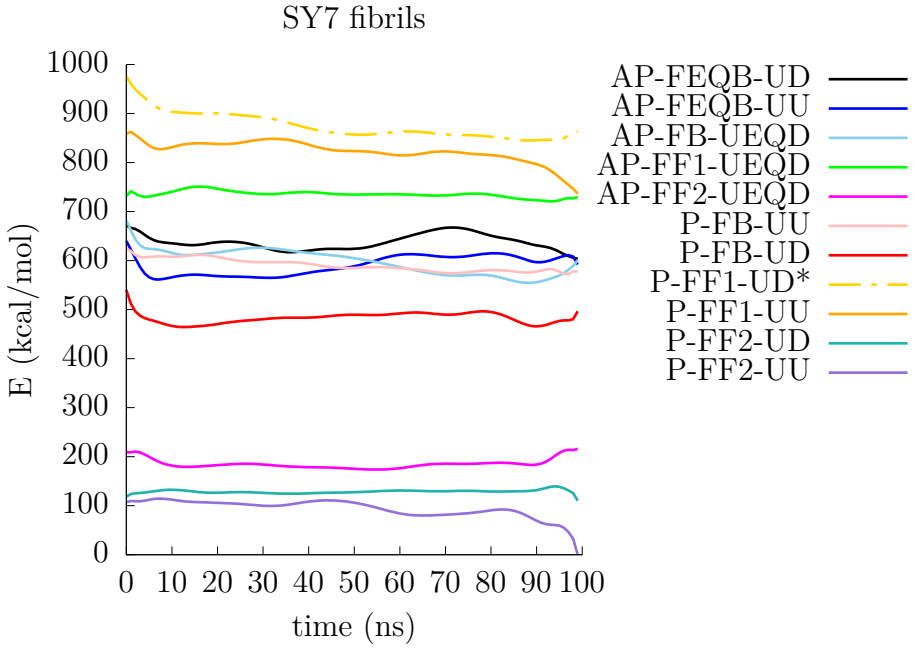


Figure S 4: Relative energies of SY7 fibril models.

The most stable architectures are P-FF2-UU, P-FF2-UD and AP-FF2-UEQD, in all cases serine residues are at the interface and tyrosines exposed to the solvent. Structure labeling corresponds to that of Figure 1 of the main text.

5.3 Glycine-Tyrosine systems - GY7

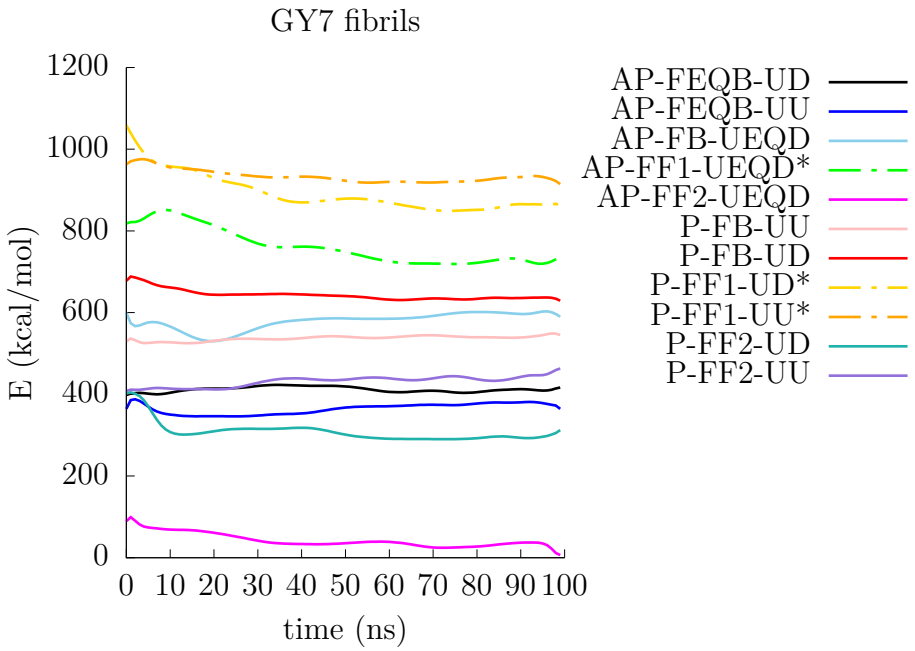
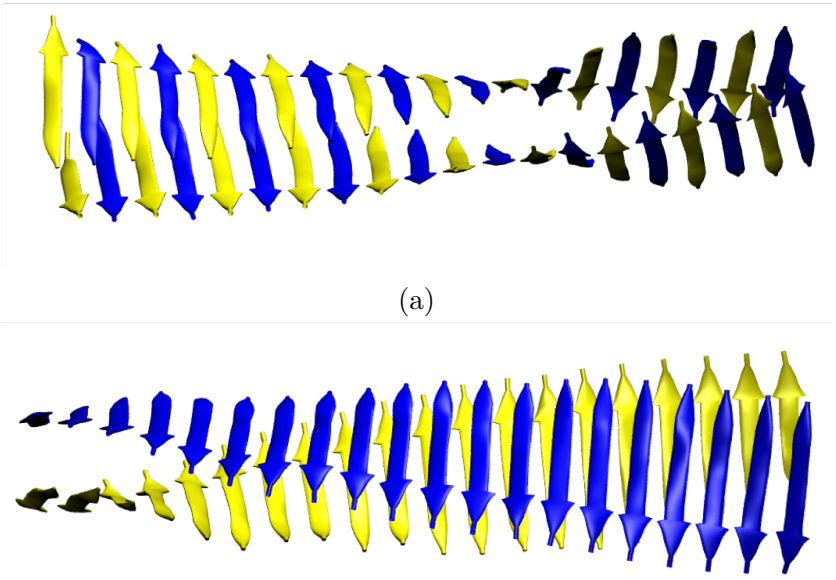


Figure S 5: Relative energies of GY7 fibril models.

The most stable architecture is AP-FF2-UEQD, with glycine residues at the interface and tyrosines exposed to the solvent.

6 NCI analysis



(a)

(b)

Figure S 6: Space partition for the a) lateral and b) intersheet interactions of the heptapeptide fibril models. Fragment 1 is represented in yellow and fragment 2 in blue.

7 Twist angles of NY7, SY7 and GY7

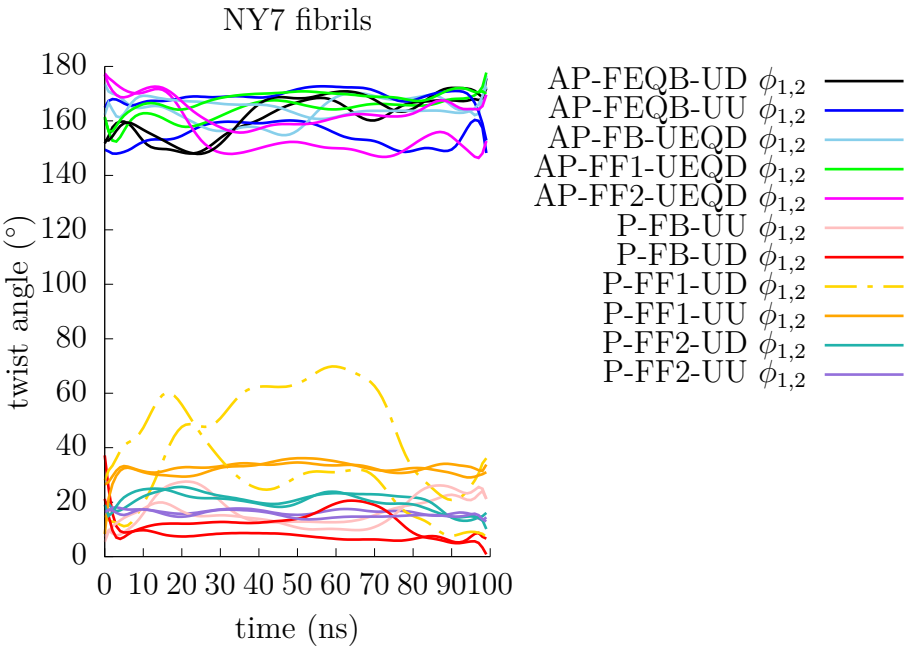


Figure S 7: NY steric zipper models twist angle.

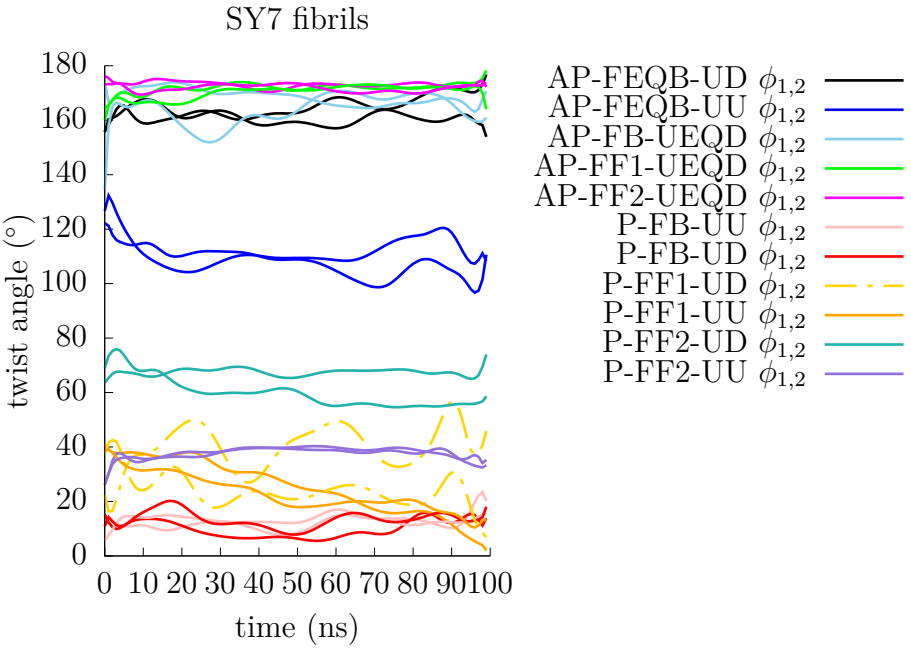


Figure S 8: SY steric zipper models twist angle.

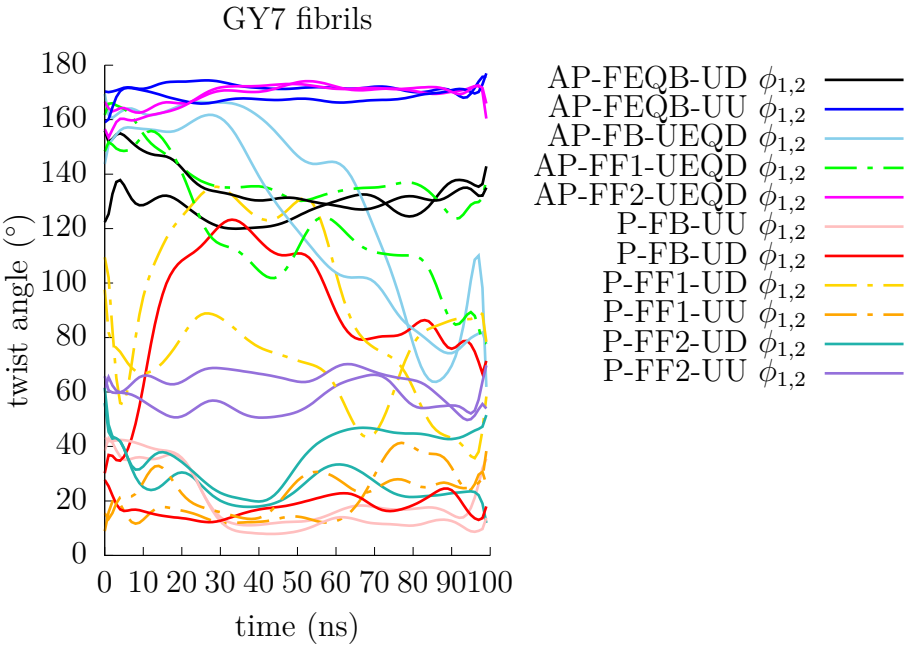
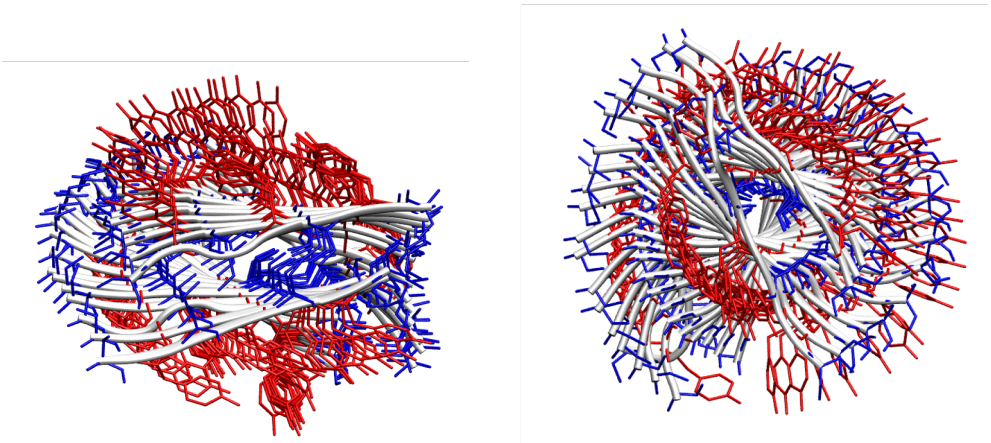


Figure S 9: GY steric zipper models twist angle.



(a) (b)

Figure S 10: a) SY7-P-FF2-UU and b) SY7-P-FF2-UD structures after 100 ns of molecular dynamics; view along the fibril growth axis.

name	BB l	avgd	BB-SC l	avgd	SC HB l	avgd	NCI vdw l	NCI a l	BB-SC i	avgd	SC HB i	avgd	NCI vdw i	NCI a i	twist	tilt
GY7-AP-FEQB-UD	95	2.88	1	2.74	0	-	181.51	30.88	17	2.77	0	-	90.04	10.50	131.59	4.65
GY7-AP-FEQB-UU	143	2.88	9	2.79	0	-	199.40	36.08	16	2.78	0	-	99.80	10.81	169.98	6.02
GY7-AP-FB-UEQD	97	2.87	2	2.77	0	-	201.81	30.41	22	2.76	0	-	78.82	8.58	128.48	7.49
GY7-AP-FF1-UEQD	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
GY7-AP-FF2-UEQD	137	2.87	0	-	0	-	242.52	35.63	0	-	0	-	104.69	7.65	169.40	1.97
GY7-P-FB-UU	16	2.87	57	2.72	0	-	222.90	31.92	57	2.72	0	-	82.45	10.59	19.41	4.57
GY7-P-FB-UD	56	2.86	6	2.75	0	-	209.11	30.18	7	2.75	0	-	76.92	8.61	54.12	4.86
GY7-P-FF1-UD	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
GY7-P-FF1-UU	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
GY7-P-FF2-UD	99	2.87	0	-	0	-	253.05	31.87	0	-	0	-	102.37	5.80	31.33	5.99
GY7-P-FF2-UU	78	2.88	0	-	0	-	231.20	29.66	0	-	0	-	90.84	5.51	60.35	3.87
SY7-AP-FEQB-UD	113	2.87	66	2.75	0	-	195.59	41.09	0	-	20	2.80	72.31	9.11	162.87	4.75
SY7-AP-FEQB-UU	175	2.87	35	2.74	0	-	214.68	40.80	0	-	6	2.81	56.03	4.68	109.84	6.62
SY7-AP-FB-UEQD	141	2.87	36	2.78	3	2.76	220.17	40.30	8	2.77	50	2.80	76.47	11.79	166.20	6.99
SY7-AP-FF1-UEQD	164	2.88	0	-	0	-	229.41	41.59	0	-	24	2.83	57.84	7.72	171.13	1.78
SY7-AP-FF2-UEQD	171	2.88	18	2.71	14	2.79	268.95	47.85	19	2.72	26	2.79	109.10	16.15	172.43	2.51
SY7-P-FB-UU	94	2.83	1	2.76	0	-	252.34	32.47	36	2.77	60	2.77	93.69	17.16	12.71	8.15
SY7-P-FB-UD	21	2.86	36	2.79	0	-	257.11	35.38	0	-	148	2.75	81.36	16.70	11.63	2.54
SY-P-FF1-UD	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SY7-P-FF1-UU	76	2.85	0	-	0	-	246.62	33.63	0	-	142	2.81	83.13	12.79	24.19	1.51
SY7-P-FF2-UD	0	-	0	-	17	2.77	312.97	22.94	121	2.70	34	2.77	134.89	21.57	63.66	4.27
SY7-P-FF2-UU	107	2.86	19	2.76	34	2.72	289.97	36.61	38	2.76	138	2.72	114.81	21.09	37.80	1.94
NY7-AP-FEQB-UD	134	2.87	52	2.79	0	-	231.25	44.03	0	-	17	2.74	56.08	7.67	161.82	4.75
NY7-AP-FEQB-UU	171	2.87	42	2.73	1	2.86	229.14	42.07	0	-	8	2.79	59.03	6.99	161.91	3.08
NY7-AP-FB-UEQD	161	2.87	20	2.73	12	2.84	229.59	45.46	0	-	50	2.74	63.12	11.41	164.25	4.31
NY7-AP-FF1-UEQD	175	2.87	2	2.82	6	2.84	248.38	46.14	0	-	26	2.83	57.70	7.33	166.12	1.70
NY7-AP-FF2-UEQD	141	2.87	11	2.84	47	2.84	251.06	48.19	5	2.84	72	2.84	69.32	14.91	159.06	2.18
NY7-P-FB-UU	63	2.86	26	2.76	23	2.85	277.41	45.79	4	2.79	40	2.73	59.89	9.95	16.63	1.39
NY7-P-FB-UD	64	2.87	2	2.87	61	2.83	265.09	42.46	0	-	46	2.85	64.33	7.90	10.11	5.79
NY7-P-FF1-UD	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
NY7-P-FF1-UU	117	2.86	0	-	19	2.85	272.19	46.09	0	-	144	2.81	84.18	12.29	32.46	1.63
NY7-P-FF2-UD	108	2.87	0	-	128	2.84	274.52	49.48	0	-	118	2.86	64.45	16.35	20.56	1.27
NY7-P-FF2-UU	68	2.87	0	-	166	2.82	285.66	53.37	0	-	62	2.87	83.25	17.54	15.94	1.16

Table S 1: BB l/i: intra-sheet (l) and inter-sheet (i) backbone H bonds; BB-SC l/i: intra-sheet (l) and inter-sheet (i) backbone-side chain H bonds; SC HB l/i: intra-sheet (l) and inter-sheet (i) side chain H bonds; Criterion: present in more than 50% of the trajectory. twist angle and tilt angle in degrees. NCI vdw/a l/i: intra-sheet (l) and inter-sheet (i) van der Waals (vdw) and attractive (a) integrals. Most stable structure(s) colored in blue and unstable structures (that disaggregate along the MD and not further analyzed) in red.

8 Validation

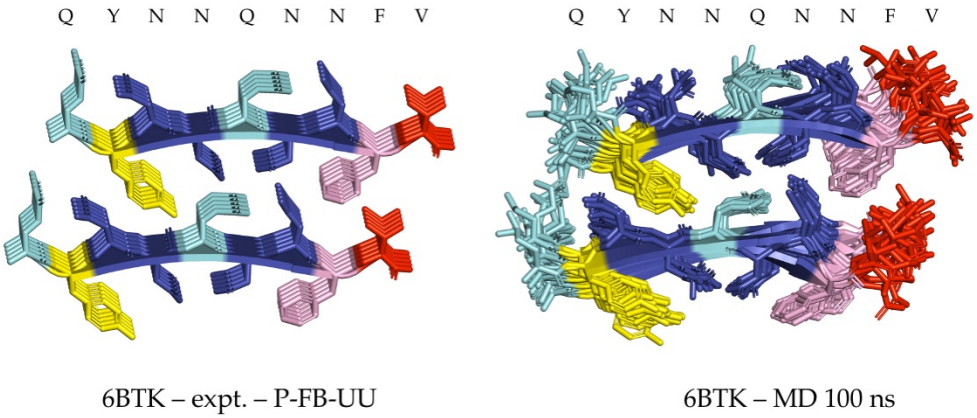


Figure S 11: Experimental structure and last frame of a 100 ns MD simulation of PDB 6BTK.

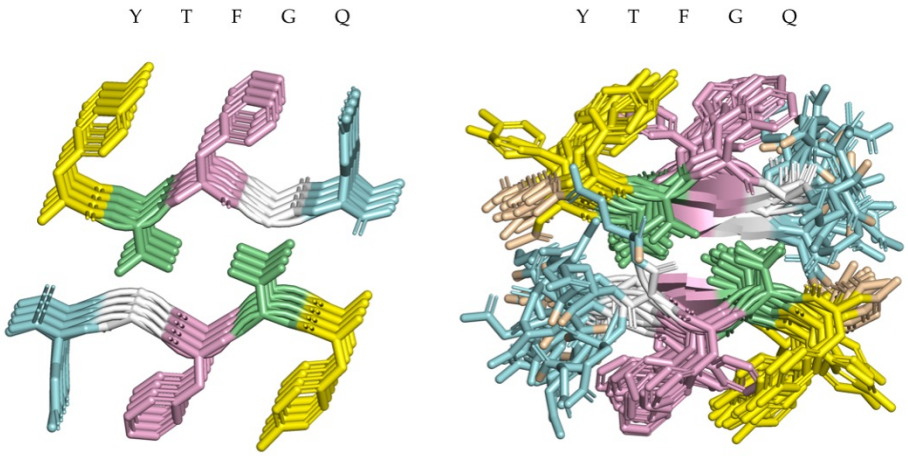


Figure S 12: Experimental structure and last frame of a 100 ns MD simulation of PDB 6DIY.

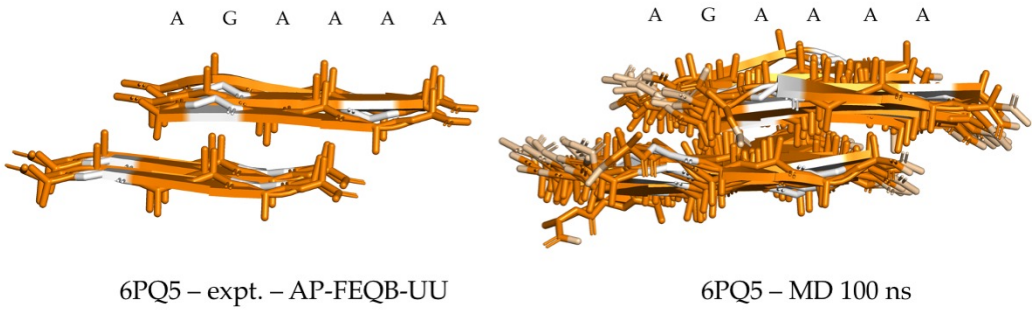


Figure S 13: Experimental structure and last frame of a 100 ns MD simulation of PDB 6PQ5.

8.1 Intersheet distances along the 100 ns molecular dynamics simulations of NY7-P-FF2-UU, SY7-P-FF2-UU, GY7-AP-FF2-UEQD and the systems of the validation set

The procedure for computing intersheet distances in our flexibile steric zipper is discussed in the main text. Figure S14 provides a visual aid. The steric zipper is represented in black lines, and α-carbons as dots. The α-carbons represented in magenta (for clarity those of an individual strand) are the ones on which the distance analysis is performed. For each magenta dot, we find the closest yellow dot on the opposite sheet, generating atom pairs. The red arrow corresponds to the pair with the largest distance (red histogram bars in Figure 7 of the main text), the blue arrow to the shortest (blue histogram bars in Figure 7 of the main text), and the average of the distances represented by all arrows yields the mean value (green histogram bars in the main text).

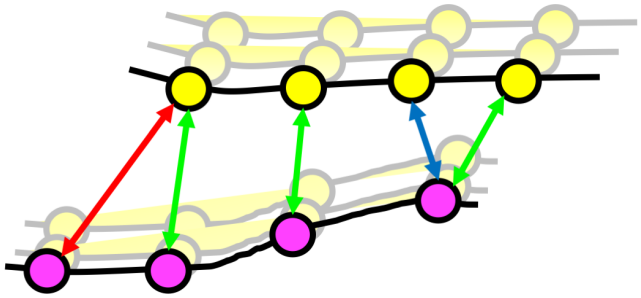


Figure S 14: Graphical representation of the approach followed to compute interhseet distances along the MD trajectories.

The evolution of these maximum, minimum and mean distances along the molecular trajectories of NY7-P-FF2-UU, SY7-P-FF2-UU, GY7-AP-FF2-UEQD and the systems of the validation set is shown in the following figures.

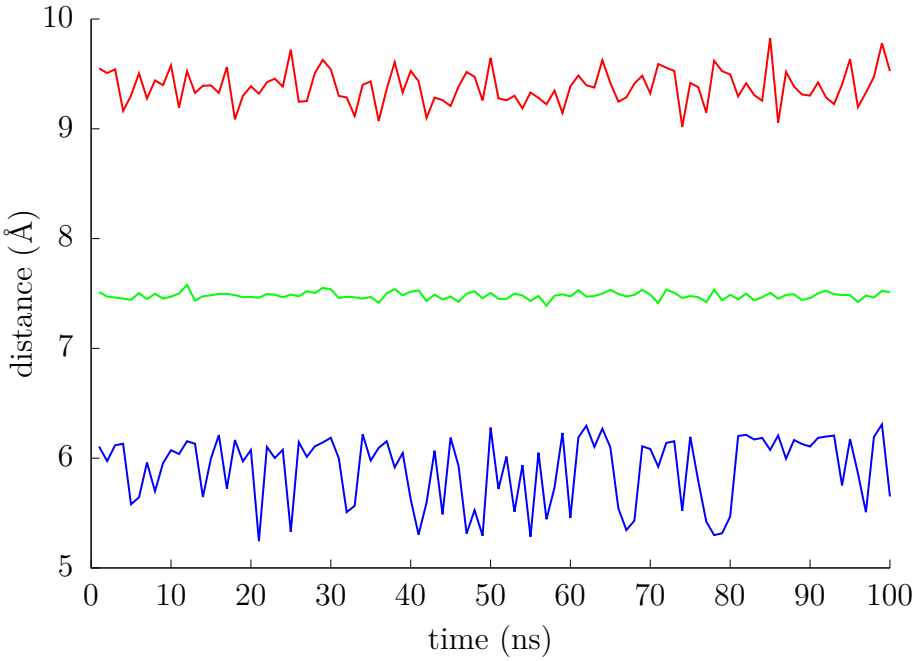


Figure S 15: Minimum (blue), mean (green) and maximum (red) intersheet distance computed along the molecular dynamics trajectory of NY7-P-FF2-UU.

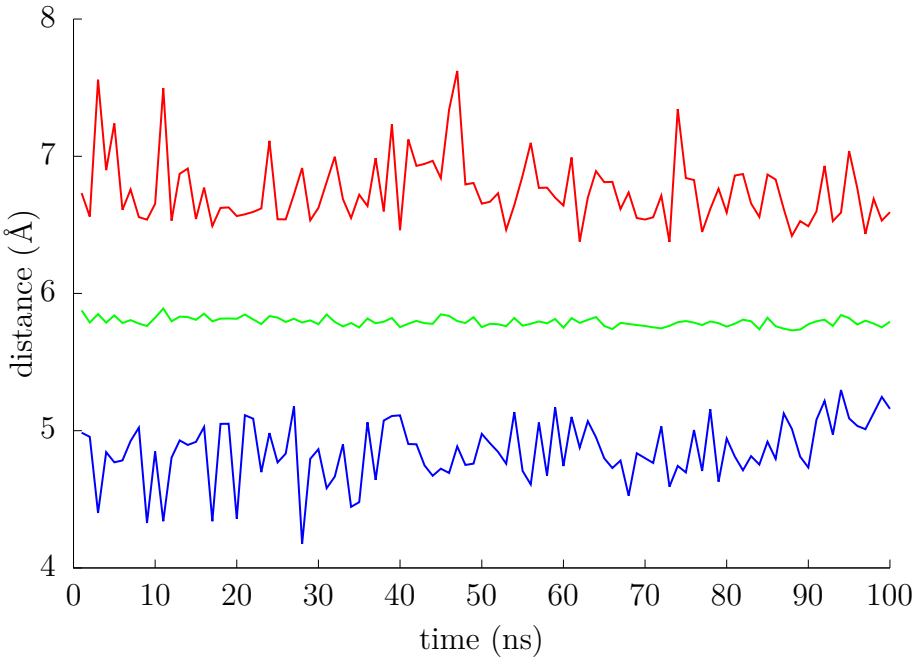


Figure S 16: Minimum (blue), mean (green) and maximum (red) intersheet distance computed along the molecular dynamics trajectory of SY7-P-FF2-UU.

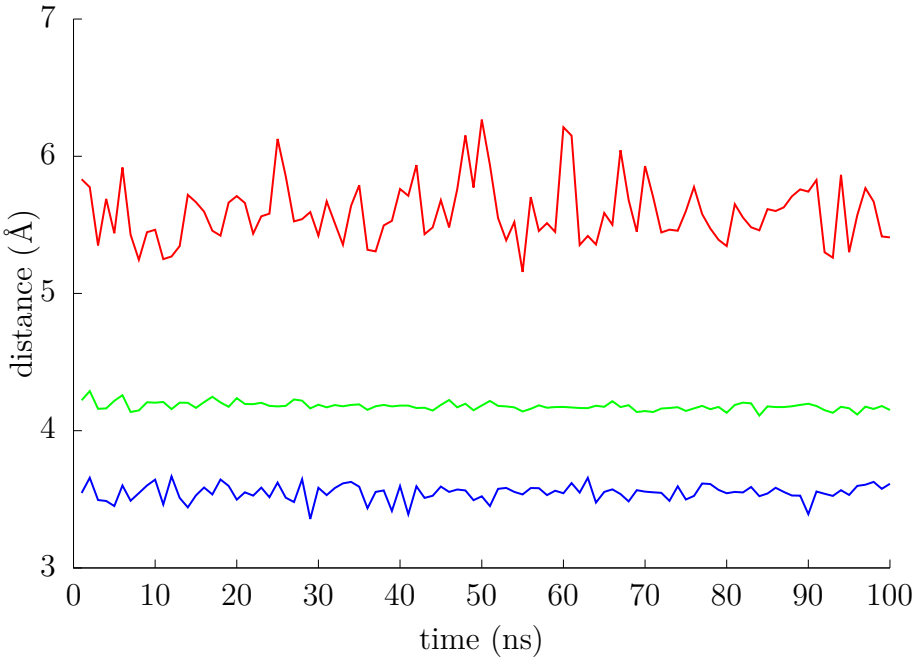


Figure S 17: Minimum (blue), mean (green) and maximum (red) intersheet distance computed along the molecular dynamics trajectory of GY7-AP-FF2-UEQD.

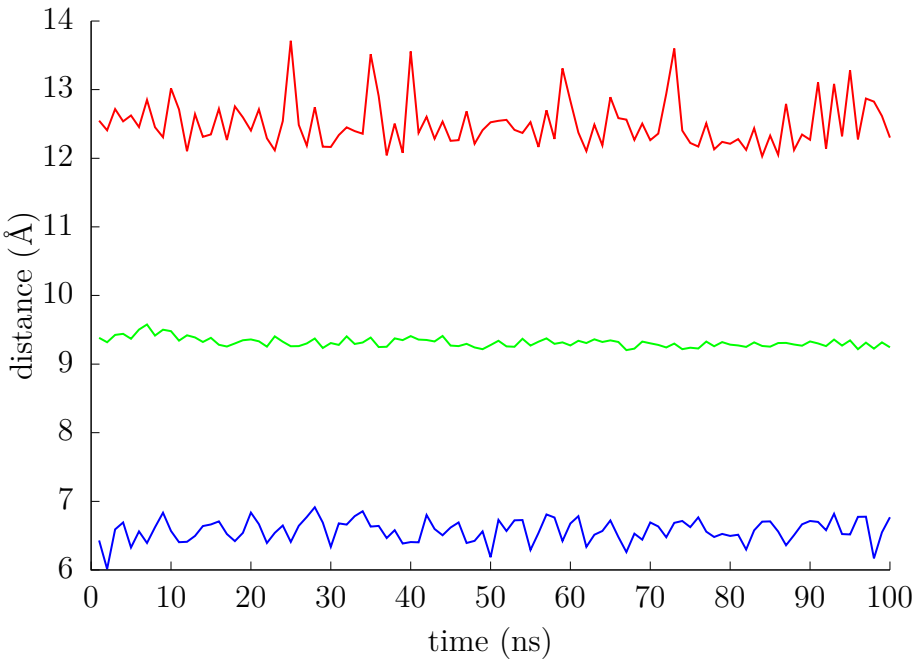


Figure S 18: Minimum (blue), mean (green) and maximum (red) intersheet distance computed along the molecular dynamics trajectory of validation structure 6BTK.

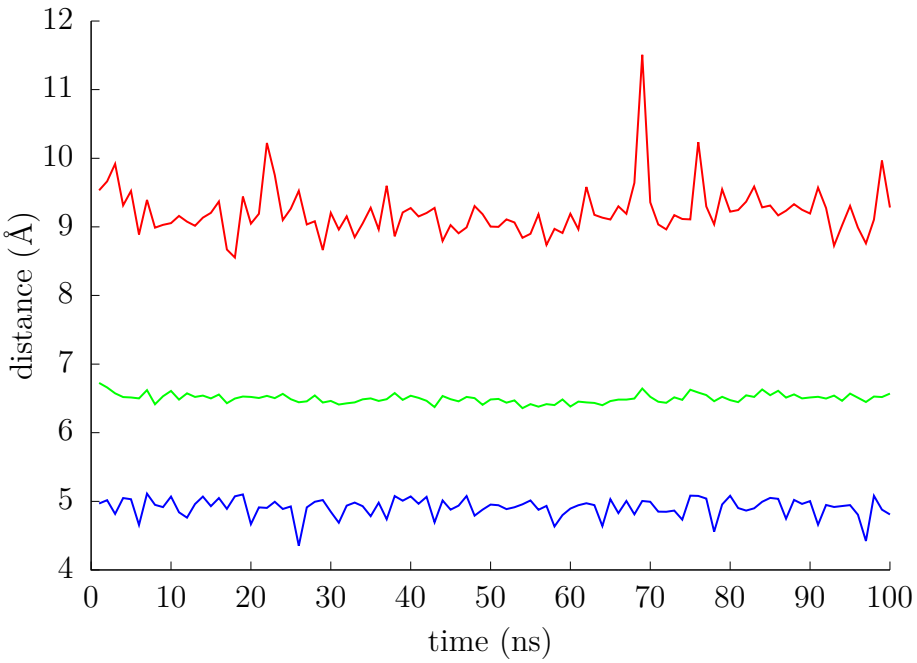


Figure S 19: Minimum (blue), mean (green) and maximum (red) intersheet distance computed along the molecular dynamics trajectory of validation structure 6DIY.

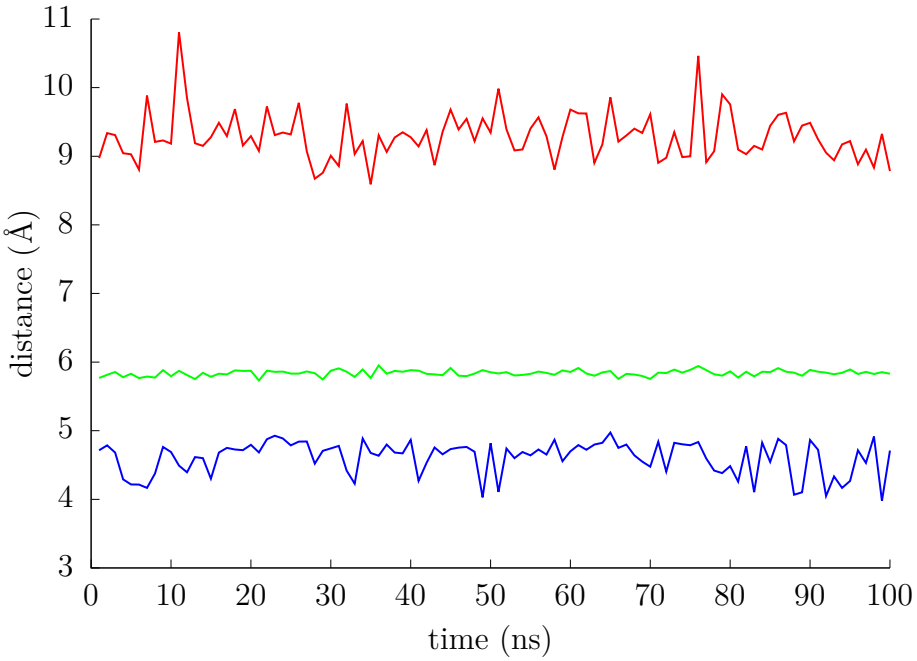


Figure S 20: Minimum (blue), mean (green) and maximum (red) intersheet distance computed along the molecular dynamics trajectory of validation structure 6PQ5.