Supplementary Information

Emergence of Alternative structures in Amyloid beta 1-42 Monomeric Landscape by N-terminal Hexapeptide Amyloid Inhibitors

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Model and Methods

Molecular dynamics simulation at various resolutions\(^1\)\(^-\)\(^6\) serves as a useful tool for the structural characterization of intrinsically disordered peptides, such as the Amyloid beta (Aβ). In this study we have performed extensive Replica Exchange Molecular Dynamics\(^7\)\(^,\)\(^8\) (REMD) simulations to generate conformational ensemble of a single Aβ\(_{42}\) monomer in presence of a WT, A2V, or A2T Aβ\(_6\) variant. REMD is an enhanced sampling technique that has been successfully used to generate robust structural ensembles for intrinsically disordered proteins, such as the Aβ peptide, that lack a single native conformation and instead exists as dynamic ensemble of rapidly interconverting conformations\(^9\)\(^-\)\(^12\). In REMD, several identical replicas (\textit{i.e.} copies) of the system are simulated in parallel over a wide range of temperature. Conformations populated at different temperatures are exchanged at frequent intervals following a Metropolis Monte Carlo criterion, so that the principle of detailed balance is satisfied. Employing this method ensures that the system does not get trapped in a local minimum on the free energy landscape\(^7\).

The following protocol was used to set up the initial structure for the REMD simulation, which is similar to what was used in our earlier published simulations of the free Aβ\(_{42}\) monomer variants\(^13\). A randomly collapsed Aβ\(_{42}\) structure was generated from a short (~10 ps) MD simulation performed at 700 K in vacuum. The collapsed structure was then solvated, charge-neutralized by adding ions, energy minimized, and equilibrated for 1 ns in an NPT ensemble (300 K and 1 atm). The structure of the short WT Aβ\(_6\) peptide was constructed using the first six residues of the full-length monomer as a template and ensuring that the phi and psi dihedral angles are consistent with a random coil structure. Next, the Aβ\(_{42}\) monomer and the WT Aβ\(_6\) hexapeptide were placed together in a 5.7 x 5.7 x 5.7 nm\(^3\) sized cubic box that contains ~5,600 water molecules (Fig. 1b, main text), resulting in an effective peptide concentration of 10 mM. The minimum
distance (heavy atom only) between Aβ42 and Aβ6 in the initial structure was at least 1.5 nm. The peptide termini were charged, and four Na\(^+\) ions were added to charge-neutralize the system. A similar protocol was employed to generate the initial solvated structure of the Aβ42 in presence of the A2V or A2T hexapeptide variant, in which the sidechain of residue 2 of the hexapeptide was accordingly mutated \textit{in silico} using the Mutate plugin of the VMD software\(^{14}\). Prior to the REMD run, all solvated systems were first subjected to a 10,000-step energy-minimization, followed by a 10 ns long equilibration run in an NPT ensemble (300 K and 1 atm). Finally, constant volume REMD simulations were run for at least 200 ns per replica. A total of 64 replicas within an exponentially distributed temperature range\(^{15}\) of 276-592.3 K were used, and replica exchange attempts were made every 4 ps, resulting into an average exchange ratio of 19% that is constant over the temperature range.

The specific temperatures at which replicas were run are:

276.0, 278.7, 281.5, 284.3, 287.2, 290.1, 293.0, 296.0, 299.0, 302.1, 305.2, 308.4, 311.7, 314.9, 318.3, 321.7, 325.1, 328.6, 332.2, 335.8, 339.5, 343.3, 347.1, 351.0, 355.0, 359.0, 363.1, 367.3, 371.6, 375.9, 380.4, 384.9, 389.5, 394.2, 399.0, 403.8, 408.8, 413.9, 419.1, 424.4, 429.8, 435.3, 440.9, 446.6, 452.5, 458.5, 464.6, 470.8, 477.1, 483.6, 490.3, 497.1, 504.0, 511.1, 518.3, 525.8, 533.4, 541.1, 549.1, 557.3, 565.7, 574.3, 583.1, 592.3.

The system was coupled to a Nosé-Hoover heat bath to maintain constant temperature between the swaps. Periodic boundary conditions were applied and the particle-mesh Ewald (PME) method was used to treat long-range electrostatics\(^{16}\). A 1.0 nm cut-off distance was used for van der Waals interactions. The bonds were constrained using LINCS\(^{17}\) and SETTLE\(^{18}\) algorithms, and an integration time-step of 2 fs was used. A combination of OPLS-AA force field\(^{19}\) and TIP3P water model\(^{20}\) was used, which has been previously reported to generate
disordered protein structural ensembles, such as Aβ, in agreement with NMR experiments\textsuperscript{21-23}. This combination is found to be well suited for simulating Aβ fragments\textsuperscript{24} and full-length Aβ peptides\textsuperscript{25}, and has been also used in our previously published Aβ monomer and dimer simulations\textsuperscript{13,26}. The simulations were performed using the GROMACS 4.5.4 software\textsuperscript{27} in IBM BlueGene/Q supercomputers.

**Conformational analysis:** The secondary structure of the peptide was calculated using the STRIDE program\textsuperscript{28}. The C\textalpha-C\textalpha tertiary contact between a pair of residues was defined by using a distance cut-off of 0.8 nm between the C\textalpha atoms. Only non-sequential contacts (|i-j| \geq 3) were considered for tertiary interactions. A salt bridge was defined using a distance cut-off of 0.32 nm between the side-chain oxygen atom of an acidic residue and the side-chain nitrogen atom of a basic residue. An inter-peptide contact was defined by using a distance cut-off of 0.5 nm (heavy atoms only). The hexapeptide was considered to be bound to the Aβ\textsubscript{42} monomer in a structure, only if \geq 25 intermolecular contacts were present. The Aβ\textsubscript{42} conformational ensemble was clustered using the Root Mean Squared Deviation (RMSD) as a similarity measure. The Daura algorithm\textsuperscript{29} with a 0.45 nm C\textalpha-RMSD cut-off between two conformations was used for clustering of the whole production ensemble (Fig. S2). All peptide structures were rendered using VMD software\textsuperscript{14}.

**Solvent Accessible Surface Area:** The hydrophobic solvent accessible surface area (SASA) was calculated using the VMD plugin with a probe radius of 1.4 Å\textsuperscript{14}. The average SASA value for the CHC-CTR β-hairpin structure was calculated using the free Aβ\textsubscript{42} (structures corresponding to regions 6 and 7 of Fig. S6). The average SASA value for CTR-hairpin structures was obtained from the largest cluster of WT-bound and A2T-bound S4 sub-populations. For the NTR-CTR β-
sheet structures, the largest cluster of WT-bound S5 and A2V-bound S4 sub-populations were used.

**Binding energy calculation:** The average binding free energies ($\Delta G_{\text{bind}}$) between Aβ42 and Aβ6 were calculated using the MM-PBSA method$^{30,31}$. In this technique, the total binding energy is a cumulative of the molecular-mechanics energy (van der Waals and electrostatics) and solvation (non-polar and polar solvation) energy terms. The MM-PBSA method does not account for the entropic contribution to binding. The non-polar solvation energy was estimated using a model based on a combination of solvent-accessible surface area and solvent accessible volume calculation$^{30,32}$. The molecular dielectric surface was defined by a probe radius of 1.4 Å. The dielectric constants of the protein interior and the aqueous environment were set to 2 and 80, respectively, and the ionic concentration set to 150 mM. Standard deviations (SD) were estimated by using a bootstrap approach, and standard errors of mean (SEM) were computed from the SD derived from an ensemble of ~30,000 structures.

**PMF analysis and clustering:** Potential of mean force (PMF, $W(X)$) was defined by the equation $W(x) = -RT \log(p(X))$, where $X$ is a set of reaction coordinates and $p(X)$ is the probability. Following reaction coordinates were defined for this purpose: (i) the total number of residues from the CHC and CTR in an extended β-strand conformation ($N_{\beta_{\text{CHC+CTR}}}$); and (ii) the number of Cα contacts between CHC and CTR ($N_{\text{Cα CHC-CTR}}$); both normalized to unity. Six sub-populations (S1 through S6) were defined on the PMF landscape that correspond to the regions having PMF energy $< -4$ kcal/mol (see Fig. 5, main text). The arbitrary boundaries used to define these sub-populations are reported in Table S3. The sub-populations that individually represent ≥10% of total production ensemble were further analyzed. An RMSD-based clustering was performed using the Daura algorithm$^{29}$ and a 0.3 nm pairwise Cα-RMSD cut-off on each of those sub-populations.
**Error analysis:** Standard errors of mean (SEM) were estimated for secondary, tertiary, and quaternary structural features, as well as for the relative population of S1-S6 states on the PMF landscape. These SEM values were obtained from standard deviations estimated by dividing the simulation data into two (or four) 35 ns long, non-overlapping blocks between 60 – 130 (or 60-200) ns. The SEM in the probability difference plots (secondary and tertiary structure analyses, Figs. 2 and 3, main text) were estimated by following the standard rule of error propagation.

**Equilibration and convergence assessment of REMD ensemble**

Along with the Root Mean Square Deviation (RMSD) analysis described in the main text (Fig. 1c), we performed the following evaluations to further validate the REMD ensemble. To ensure that the choice of initial peptide structure did not bias the final results, we checked the evolution of intermolecular distance between the centers of mass (COM) of the full-length peptide and the hexapeptide. The evolution of intermolecular distance for the 308.4 K replica is shown in Fig. S1. The interpeptide distance equilibrates to about 1.2 nm by 50 ns, and fluctuates steadily around this mean with a standard deviation of ± 0.4 nm. This observation suggests that the ensemble populated after 50 ns is independent of the initial conformation. Therefore, we considered the 60-200 ns portion of REMD trajectories for further analysis.

Next, we compared the probability distributions of (i) the radius of gyration ($R_g$); (ii) the number of intra-peptide CHC-CTR $C_\alpha$ contacts ($N_{\text{CHC-CTR}}$); and (iii) the residue-wise turn propensity of $\alpha\beta_42$ over two time intervals, 60 – 130 ns and 60 – 200 ns, in order to ensure that the simulations have reasonably converged. Results for the 308.4 K replica are shown in Fig. S1 and Table S1. For all three distributions, the overall range and the major features remain constant
between the two time-intervals. The mean \( R_g \) value is 1.04 nm, 1.11 nm, and 1.05 nm for the WT-bound, A2V-bound, and A2T-bound A\( \beta \)\(_{42} \) and remain unchanged over the two time-windows of 60–130 ns and 60–200 ns. The average number of CHC-CTR contacts is about 12 for all three hexapeptide-bound systems. The turn propensity distributions are virtually indistinguishable between the different time windows, suggesting good convergence of the REMD trajectories.

**Size and disorder of the production ensemble**

The \( R_g \) distribution of the production ensemble is distributed around the mean value of 1.06 ± 0.12 nm for free, 1.05 ± 0.07 nm for WT-bound, 1.07 ± 0.10 nm for A2V-bound, and 1.05 ± 0.08 nm for A2T-bound A\( \beta \)\(_{42} \) (Fig. S2). This value matches well with earlier experimental\(^{33}\) and simulations studies\(^{1,21,22}\) and is consistent with a collapsed globule. Interaction with WT or A2T hexapeptides increases the population around the mean \( R_g \) value, while the distribution corresponding to the A2V-bound peptide is similar to that of the free A\( \beta \)\(_{42} \) monomer. Since A\( \beta \)\(_{42} \) is an IDP, we performed a RMSD-based clustering for the A\( \beta \)\(_{42} \) ensembles to compare the structural disorder (see Methods and Fig. S2). It is interesting to observe that the population distribution of the largest 50 clusters is similar for all four A\( \beta \)\(_{42} \) systems, indicating that the overall structural heterogeneity is not strongly affected by the NTR hexapeptide binding.

**Register-shifted \( \beta \)-hairpin within A2V S5 structures**

Analysis of A2V-bound S5 structures that present 11.6% of the total ensemble reveals a \( \beta \)-strand rich population (Fig. S9). The \( \beta \)-hairpin is comprised of \( \beta \)-strands involving residues 18-22
and 27-31 and a short turn region around residues 23-26. This structure is different from the transient CHC-CTR hairpin often observed within free \(\text{A}\beta_{42}\) S6 structures (Fig. S6), as the hairpin within A2V-bound S5 \(\text{A}\beta_{42}\) shows a register shift towards C-terminus and a shorter turn. The hexapeptide mainly interacts through residues D1 and V2 with NTR, CHC or CTR residues of the \(\text{A}\beta_{42}\) monomer.

**Representative structure of S1-S6 sub-population**

The most representative structure of each significant (>10%) sub-population of free and WT/A2V/A2T bound \(\text{A}\beta_{42}\) is shown in Figure S10. While the free and the A2V-bound peptides in S1 are overall unstructured, the A2T-bound S1 structure has the preCHC/CHC helix. The WT-bound S2 structure also acquires the preCHC/CHC helix conformation, while the A2V-bound S2 remains unstructured. Only the A2T-bound peptide shows a significant population of the S3 region and frequently visits the preCHC/CHC helix conformation. The free \(\text{A}\beta_{42}\) structure from the S4 region forms a \(\beta\)-hairpin with residues 23-40 with a short helical turn in the CHC region. While the WT-bound and A2T-bound S4 structures are comprised of the CTR-hairpin, A2V-bound S4 structure forms the NTR-CTR \(\beta\)-sheet. Within S5 sub-population, WT-bound structure also forms the NTR-CTR \(\beta\)-sheet, while A2V-bound structure acquires the register-shifted \(\beta\)-hairpin conformation. The S6 \(\text{A}\beta_{42}\) structure (bound or free) consistently exhibit the disease-implicated CHC-CTR hairpin conformation. Taken together, our analysis confirms the sequence-dependent effect of the hexapeptide interaction on the \(\text{A}\beta_{42}\) structure.
Figure S1:

REMD equilibration and convergence analysis. Results are shown for the replica corresponding to 308.4 K. Moving averages of 1 ns are shown. (a) Intermolecular distance (in nm) between the centers of mass (COM) of Aβ42 and Aβ6 as a function of simulation time (in ns). The raw data (WT-bound: light brown,
A2V-bound: light green, A2T-bound: light blue) are also plotted. (b) Probability distribution of radius of gyration, \( R_g \) (in nm) of \( \beta_42 \). (c) Probability distribution of number of intra-peptide CHC-CTR \( \alpha \) contacts, \( N_{CHC-CTR} \), within \( \beta_42 \). (d) Residue-wise turn propensity (in %) of \( \beta_42 \). Standard errors of mean were estimated by dividing the data into two or four 35 ns long blocks (see Methods). Results for 60-130 ns are shown in black and those for 60-200 ns are shown in red. Results corresponding to WT-bound, A2V-bound, and A2T-bound \( \beta_42 \) are shown in left, center and right panel, respectively.

Figure S2:

(a) Probability distribution of radius of gyration, \( R_g \), of \( \beta_42 \), as estimated from the production ensemble, and (b) Population distribution of largest 50 clusters of \( \beta_42 \) structures, as obtained using a RMSD-based clustering of the production ensemble using a pairwise \( \alpha \) RMSD cut-off of 0.45 nm.
Figure S3:

Secondary structure analysis of Aβ42. (a) Overall population (in %) of secondary structural elements (C =
coil, T = turn, E = β-strand, B = β-bridge, H = α-helix, G = 310-helix, I = π-helix). (b-d) Residue-wise population distribution (in %) of secondary structure elements in (b) WT-bound, (c) A2V-bound, and (d) A2T-bound Aβ42.
Figure S4:
Secondary structure analysis of $\alpha\beta_6$. (a-c) Residue-wise population distribution (in %) of secondary structure elements for the (a) WT, (b) A2V, and (c) A2T hexapeptide.

Figure S5:
Tertiary contact map of hexapeptide-bound $\alpha\beta_{42}$ monomer. (a-c) Ensemble-averaged intramolecular $C_\alpha$ contact map (upper triangles) for (a) WT-bound, (b) A2V-bound, and (c) A2T-bound $\alpha\beta_{42}$. Only non-sequential contacts, i.e., $|i - j| \geq 3$, are shown. Associated standard error values (see Methods) are displayed in the respective lower triangles.
Figure S6:

Structural diversity within the S6 sub-population of free $\alpha_\beta_{42}$ monomer. The PMF plot of free $\alpha_\beta_{42}$ is shown at bottom right. The seven structures correspond to seven regions (marked 1 to 7) with PMF value $< -4$ kcal/mol. Most representative structure of the largest cluster is shown.
Figure S7:

Additional snapshots of alternative Aβ_{42} structures emerging due to hexapeptide binding. (a) Overall unstructured conformations (A2V-bound S1 and S2 states). (b) preCHC/CHC helix conformations (WT-bound S2 state). (b) CTR-hairpin conformations (WT-bound and A2T-bound S4). (c) NTR-CTR β-sheet conformations (WT-bound S5 and A2V-bound S4). An RMSD-based clustering with 0.3 nm pairwise C\textalpha-RMSD cut-off was performed for each sub-population. Representative structures from largest clusters are displayed. Relative population (in %) of the corresponding cluster within each state is reported in parenthesis. Peptides are displayed using cartoon representation. The Aβ_{42} peptide is colored according to the color scheme shown in Fig. 1a, while the Aβ_{6} peptide is colored in red. Different orientations of Aβ_{6} within each cluster are shown. Aβ_{42} residues that are within 0.4 nm (heavy atoms only) of the hexapeptide are displayed in licorice representation.
Figure S8:

Residue-wise secondary structure profile, and ensemble-averaged intramolecular $C\alpha$ contact map of the hexapeptide-bound Aβ$_{42}$ monomer with atypical structural features.
Figure S9: Structural Characterization of +A2V S5 sub-population. (a, b) Representative conformation of the two largest clusters (with 26.7% and 10% population), as extracted using a RMSD-based clustering. (c) Residue-wise secondary structure profile and (d) ensemble-averaged intramolecular Ca contact map of Aβ42.
Figure S10: Representative structures from each sub-population S1 – S6, that is populated above 10%. The color code is the same as that used in Fig. S7.
Table S1: REMD convergence assessment, as estimated from results (mean ± standard deviation) obtained over 60-130 ns and 60-200 ns time-window.

|          | +WT       | +A2V      | +A2T      |
|----------|-----------|-----------|-----------|
| R_0 (nm) | 1.04 ± 0.07 | 1.04 ± 0.08 | 1.12 ± 0.13 | 1.11 ± 0.11 | 1.05 ± 0.08 | 1.05 ± 0.07 |
| N_CHC-CTR| 13 ± 4    | 12 ± 4    | 13 ± 5    | 12.5 ± 5   | 12 ± 3      | 12 ± 3      |
| Turn (%) | 51.8 ± 2.8 | 50.1 ± 2.6 | 52.7 ± 2.6 | 50.7 ± 2.6 | 52.1 ± 2.9  | 50.7 ± 3.0  |

Table S2: The total interpeptide binding free energy, as well as contribution of individual energy component, as estimated using the MM-PBSA method (in kcal/mol; ± standard error of mean). ΔE_{vdW} = van der Waals; ΔE_{elec} = electrostatic; ΔE_{solv} = polar solvent; ΔE_{SASA} = solvent-accessible surface area; ΔE_{SAV} = solvent-accessible volume terms. ΔG_{bind} = total binding free energy.
Table S3: Boundaries of S1-S6 sub-populations on the PMF landscape.

|        | S1               | S2               | S3               | S4               | S5               | S6               |
|--------|------------------|------------------|------------------|------------------|------------------|------------------|
| Np<sub>CHC-CTR</sub> range | 0.00 – 0.06      | 0.00 – 0.06      | 0.00 – 0.06      | 0.12 – 0.42      | 0.12 – 0.42      | 0.29 – 0.77      |
| Nc<sub>CHC-CTR</sub> range | 0.00 – 0.15      | 0.15 – 0.41      | 0.41 – 0.74      | 0.00 – 0.25      | 0.25 – 0.41      | 0.41 – 0.96      |

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