Supporting Information

Elucidating important sites and the mechanism for amyloid fibril formation by coarse-grained molecular dynamics

Ana Rojas, Nika Maisuradze, Khatuna Kachlishvili, Harold A. Scheraga,* Gia G. Maisuradze*

Baker Laboratory of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853-1301

*To whom correspondence may be addressed. E-mail: has5@cornell.edu; gm56@cornell.edu

Author contributions: G.G.M. designed the research; A.R., N.M., K.K., and G.G.M. performed the research; A.R., N.M., K.K., and G.G.M. analyzed the data; and A.R., H.A.S., and G.G.M. wrote the paper.

Figure Captions

Figure S1. The UNRES model of polypeptide chains. The interaction sites are peptide-bond centers (p), and side-chain ellipsoids of different sizes (SC) attached to the corresponding α-carbons with different "bond lengths", b_{SC}. The α-carbon atoms are represented by small open circles. The equilibrium distance of the $C^{\alpha}\cdots C^{\alpha}$ virtual bonds is taken as 3.8 Å, which corresponds to planar *trans* peptide groups. The geometry of the chain can be described either by the virtual-bond vectors $\mathbf{dC}_i$ ($C^{\alpha}_i \ldots C^{\alpha}_{i+1}$), i = 1, 2,…, N - 1 and $\mathbf{dX}_i$ ($C^{\alpha}_i \ldots SC_i$), i = 2, 3,…, N - 1 (represented by thick dashed arrows, where N is the number of residues, or in terms of virtual-bond lengths, backbone virtual-bond angles θ_i, i = 2, 3,…, N - 1, backbone virtual-bond-dihedral angles γ_i, i = 2, 3,…, N - 2, and the angles α_i and β_i, i = 2, 3,…, N - 1 that describe the location of a side chain with respect to the coordinate frame defined by C^{α}_{i-1}, C^{α}_i and C^{α}_{i+1}.

Figure S2. Free-energy landscapes (in kcal/mol) along the first three PCs for the free monomer aggregation trajectory. All panels illustrate the same FEL. Panel A shows all points in the 3-D FEL space with free energy < 0 (kcal/mol), in which aggregation pathway is not clearly illustrated because of strong overlapping of points corresponding to diverse energies. Panel B illustrates the same 3D FEL with only the lowest free-energy points. The 3-D FEL illustrated in panel C is the same as 3-D FEL in panel B but from the top.

Figure S3. Free-energy landscapes (in kcal/mol) along the first two PCs with representative structures at the minima for three different trajectories; i.e., (A) the free monomer binds to one of the chains of the fibril template completely; (B) the free monomer binds to two different chains of the fibril template at both parallel and antiparallel orientation; (C) the

free monomer does not bind to the fibril template at all.

Figure S4. Free-energy profiles (FEPs), $\mu(\theta)$ and $\mu(\gamma)$, along the θ and γ angles (panels A and B, respectively) for three different trajectories plotted in Figure S3. Black, red and green curves correspond to FEPs computed over the trajectories plotted in panels A, B and C of Figure S3, respectively. The black numbers pertain to FEPs along the θ and γ angles which include only residues of the loop; the red numbers pertain to FEPs along the θ and γ angles which include only residues of β-strands; the green numbers pertain to FEPs along θ and γ angles which include the residues from both loop and β-strands. The NMR-derived structural data are computed from the coordinates provided by Tycko for the structural model of an $A\beta_{(1\text{-}40)}$ (Petkova et al[13]) (blue circles at the bottom of each panel).

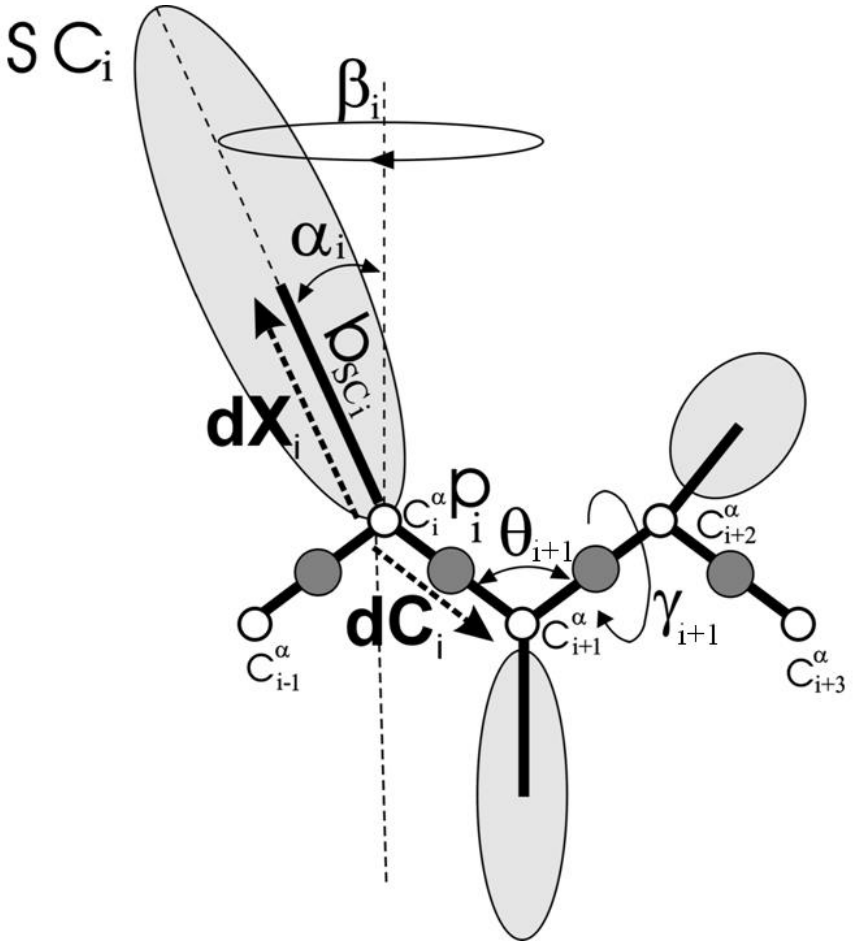

Figure S1.

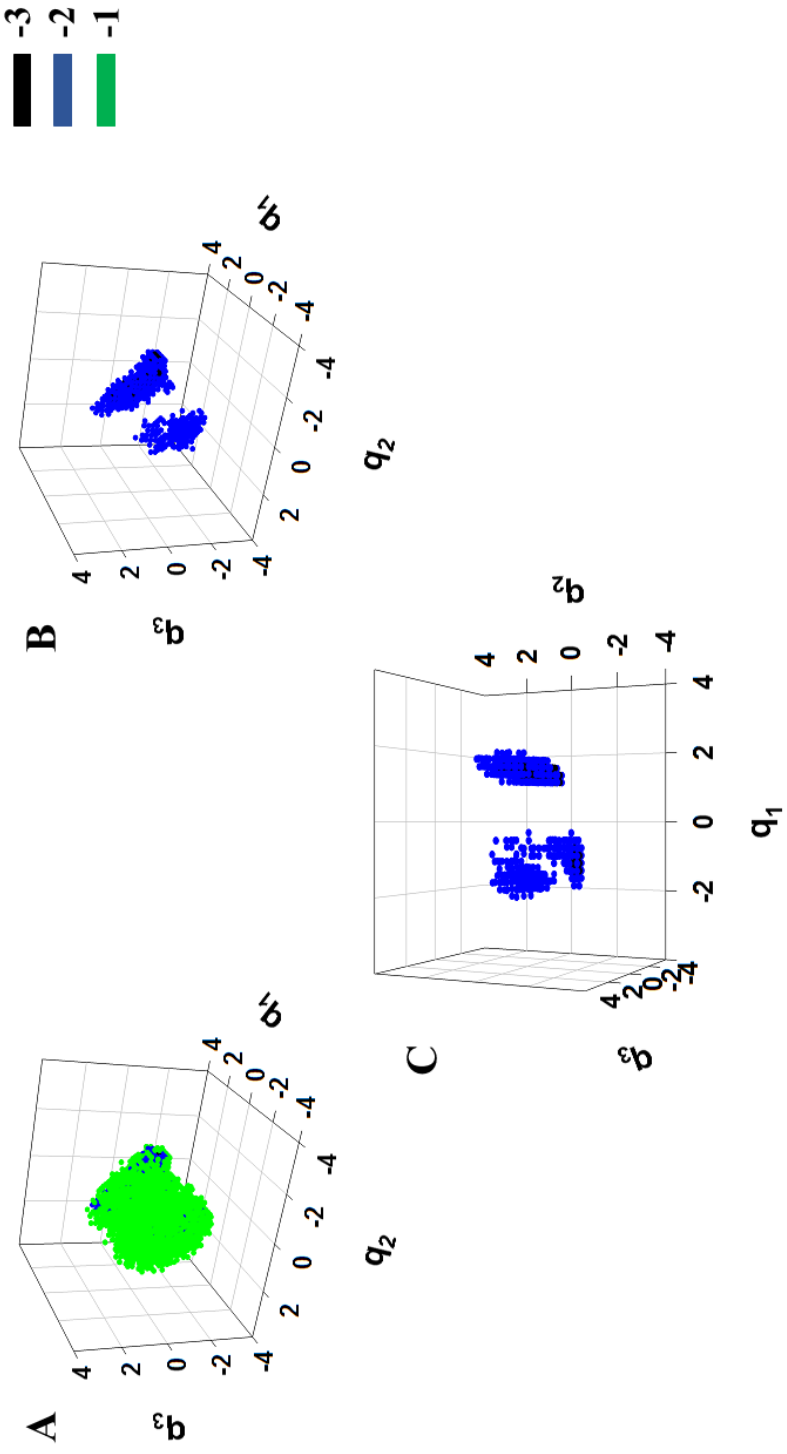

Figure S2.

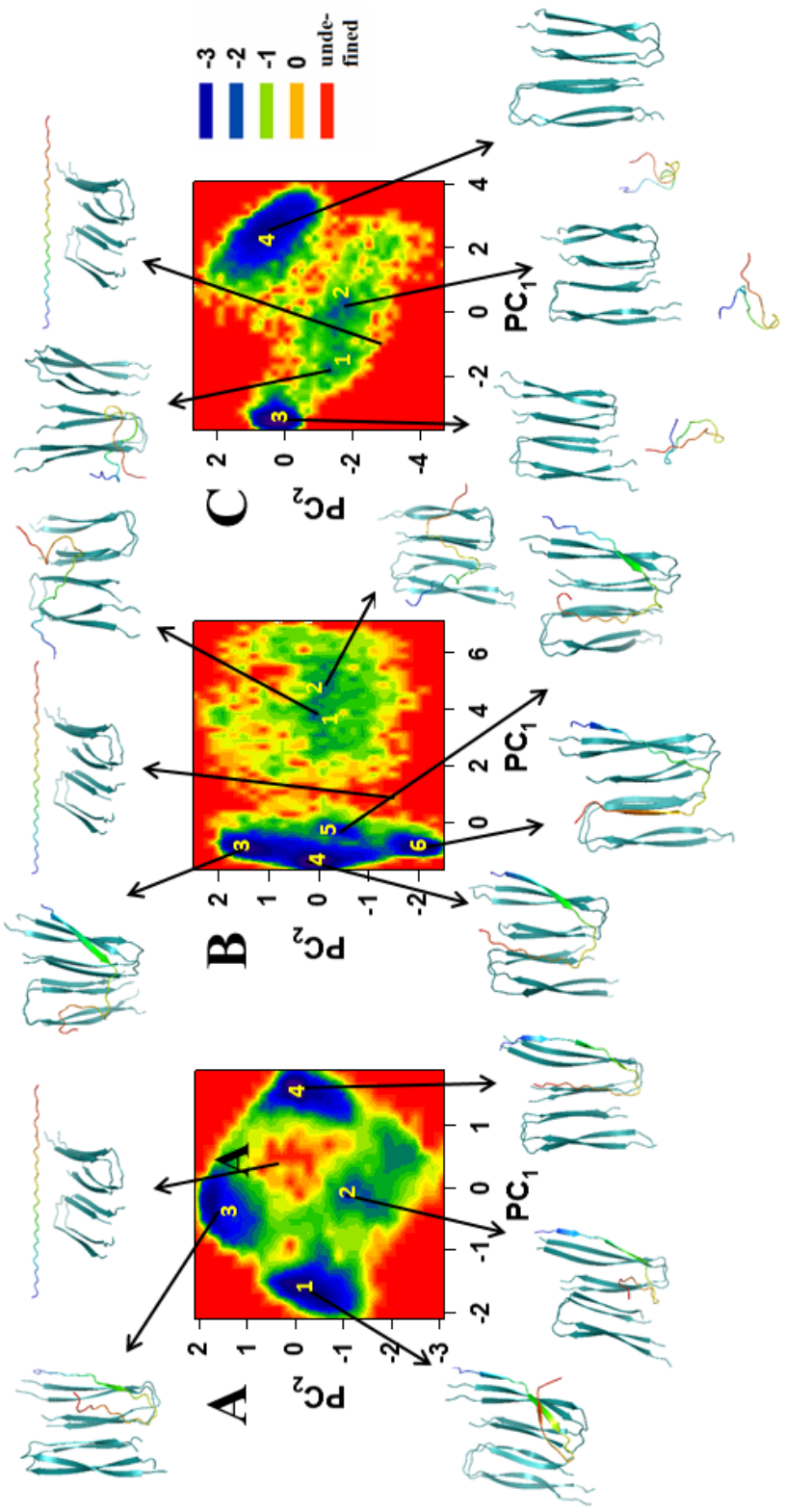

Figure S3.

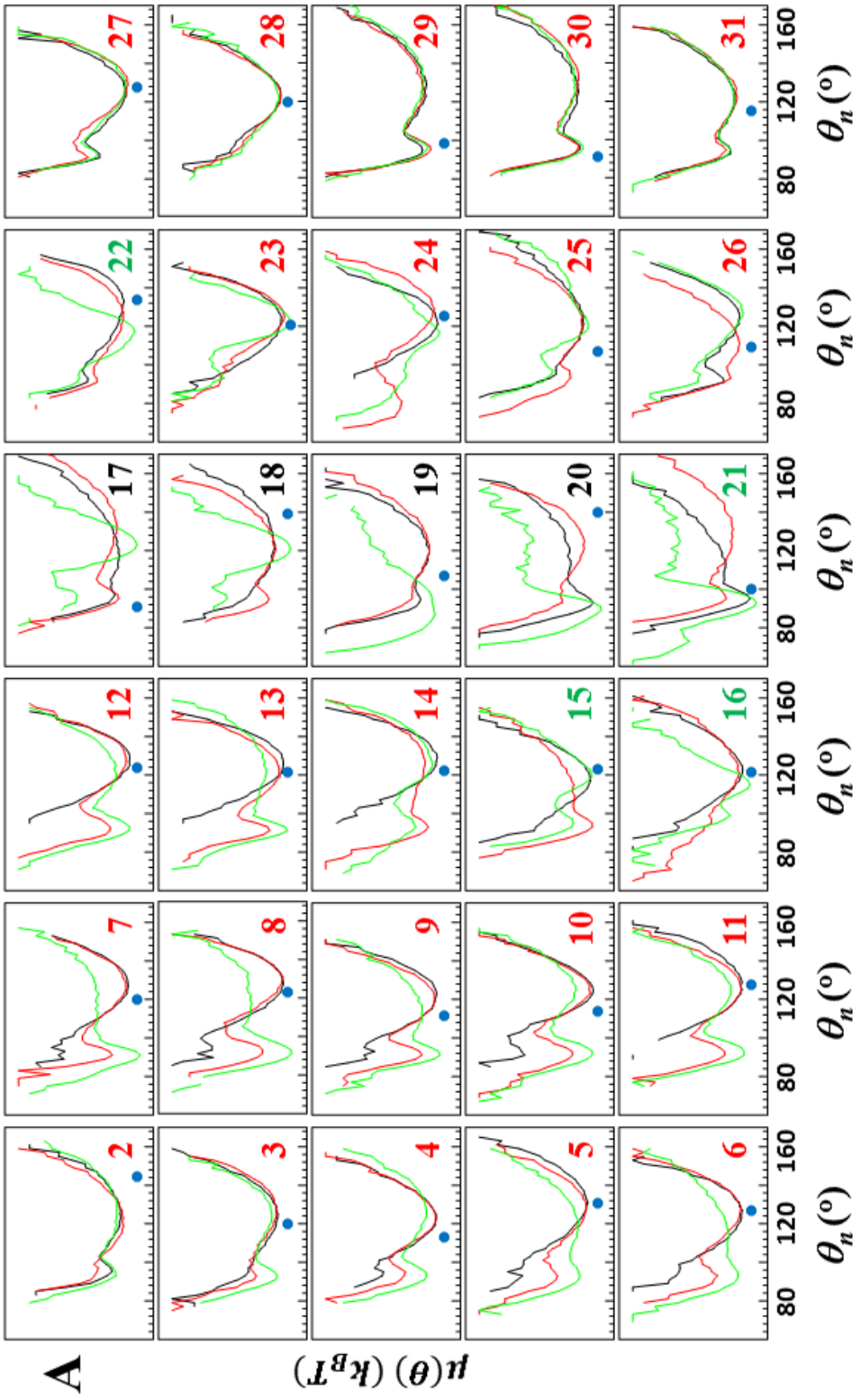
A
$\mu(\theta)$ (k_BT)
θ_n (°)
80
120
160
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Figure S4A.

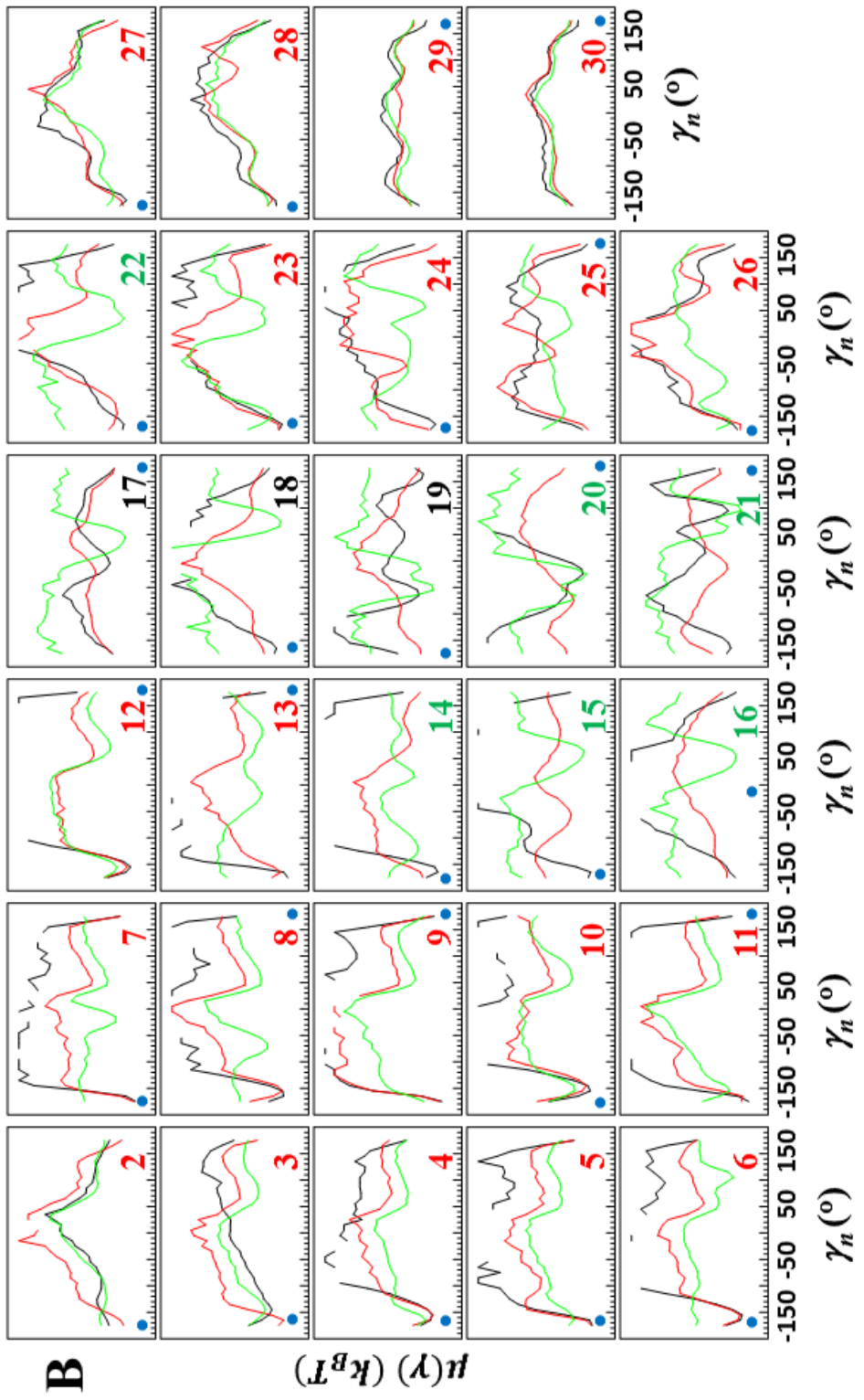
B
$\mu(\gamma)$ (k_BT)
γ_n (°)
-150 -50 50 150
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30

Figure S4B.