Supporting Information

Molecular Insights into the Misfolding and Dimerization Dynamics of the Full-length α-synuclein from Atomistic Discrete Molecular Dynamics Simulations

Yu Zhang[1], Ying Wang[1], Yuying Liu[1], Guanghong Wei[2], Feng Ding[3], Yunxiang Sun[1, 2, 3]*

[1]Department of Physics, Ningbo University, Ningbo 315211, China

[2]State Key Laboratory of Surface Physics and Department of Physics, Fudan University, Shanghai 200433, China

[3]Department of Physics and Astronomy, Clemson University, Clemson, SC 29634, USA.

*E-mail: sunyunxiang@nbu.edu.cn;

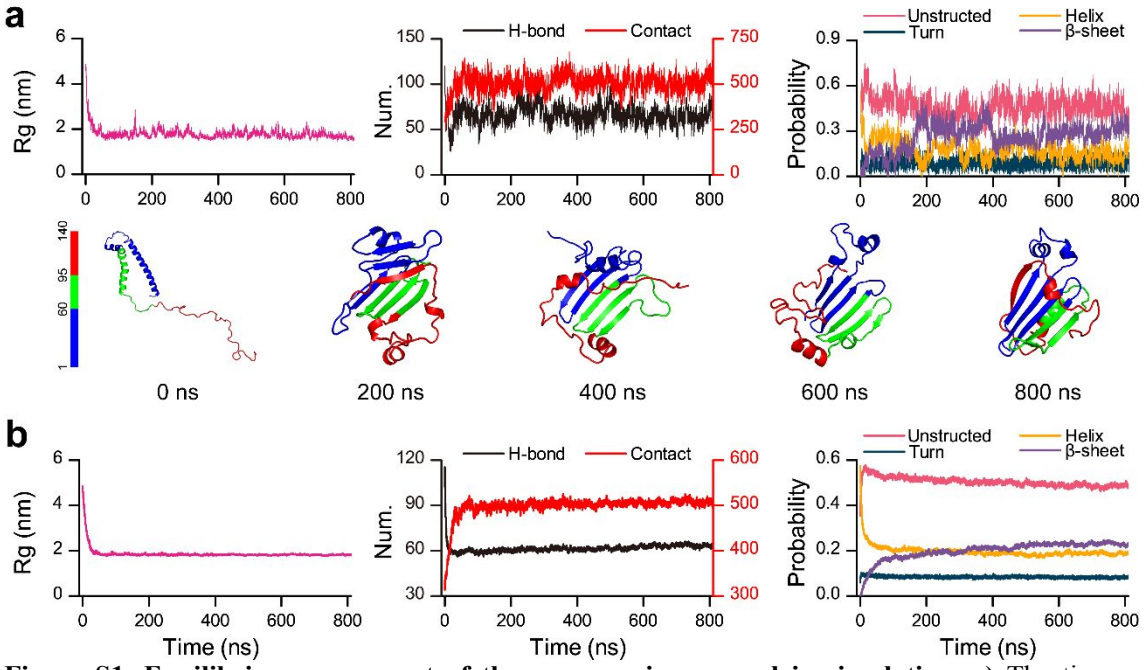

Figure S1. Equilibrium assessment of the monomeric α-synuclein simulation. a) The time evolution of the radius gyration (Rg), number of hydrogen bonds and contact, and the probability of each secondary structure. The corresponding snapshots are also present every 200 ns. Only one trajectory is randomly selected from 100 independent DMD trajectories. **b)** The radius gyration, number of hydrogen bonds and contacts, and the probability of each secondary structure averaged over all 100 independent DMD simulations.

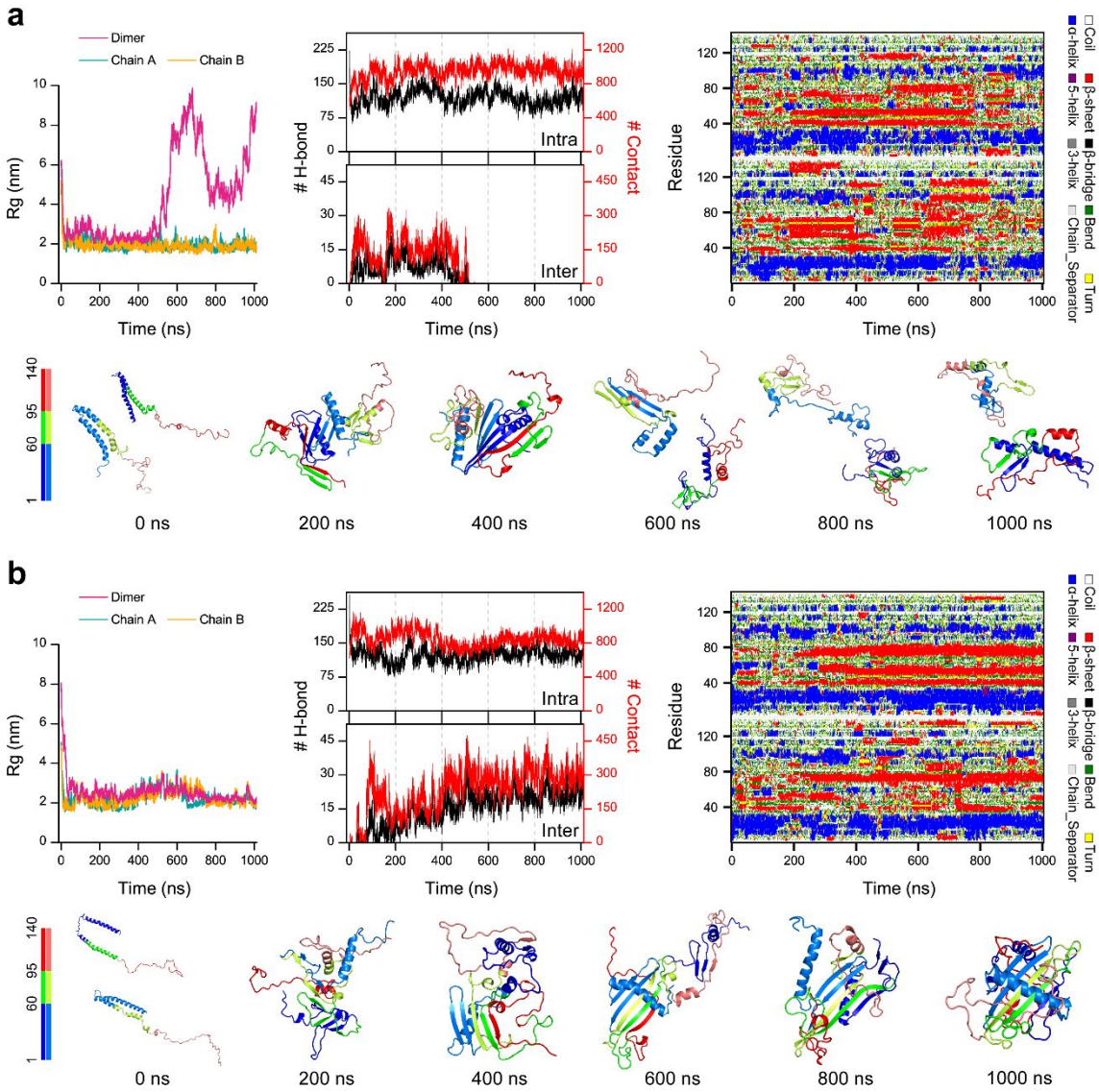

Figure S2. The dimerization and conformation dynamics analysis of α-synuclein. The dimerization and conformation dynamics monitored by the time evolution of radius gyration of each peptide and both two peptides, the total number of intra- and inter-peptide contacts and hydrogen bonds, and secondary structure of each residue. The snapshots are also present every 200 ns. Two trajectories are randomly selected from 100 dimerization DMD simulations.

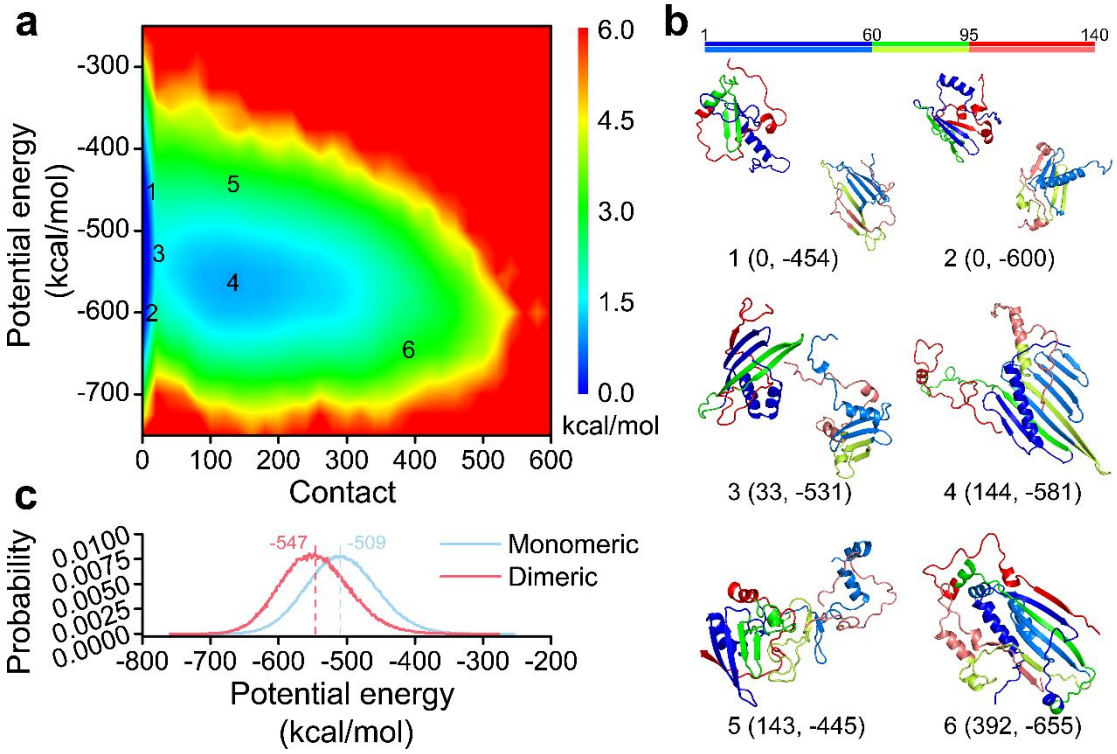

Figure S3. Dimerization free energy landscape analysis. The dimerization free energy landscape as a function of the number of inter-molecular contacts and total potential energy **a)**. Representative structures corresponding to the isolated monomers and dimers labeled in the free energy landscape are also shown **b)**. The potential energy probability distribution function of two α-synuclein peptides in monomeric and dimeric states **c).**

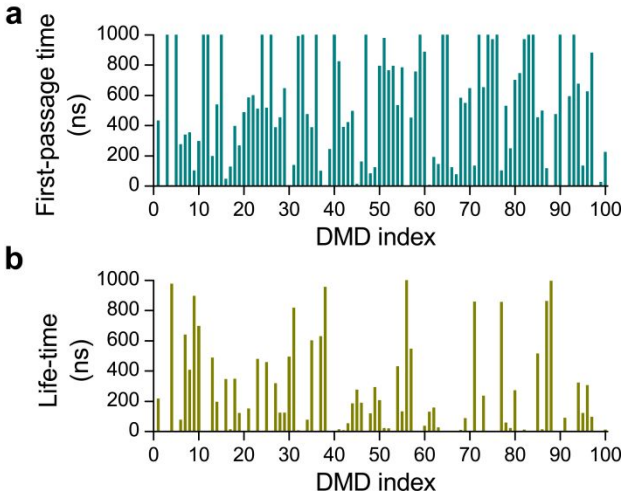

Figure S4. The dimerization time analysis of α-synuclein. The first-passage time of two isolated α-synuclein nucleated into a dimer with a number of inter-molecular contacts larger than 24 in each independent DMD simulation **a)**. If there is no dimer structure with a number of inter-molecular contacts up to 24 or more during the whole 1000 ns simulation, the first-passage time is defined as 1000 ns. The average life-time of dimeric a-synuclein within each independent DMD simulation b).

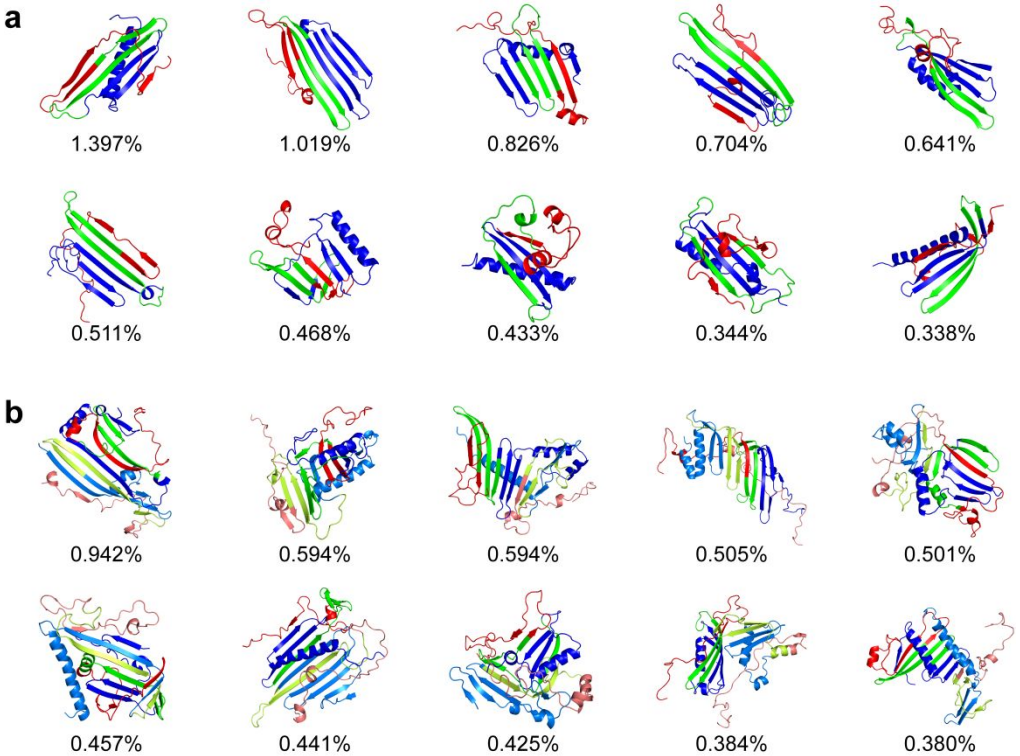

Figure S5. Representative structures of α-synuclein monomer and dimer. The central structures of top 10 most populated α-synuclein monomers and dimers using conformational cluster analysis.

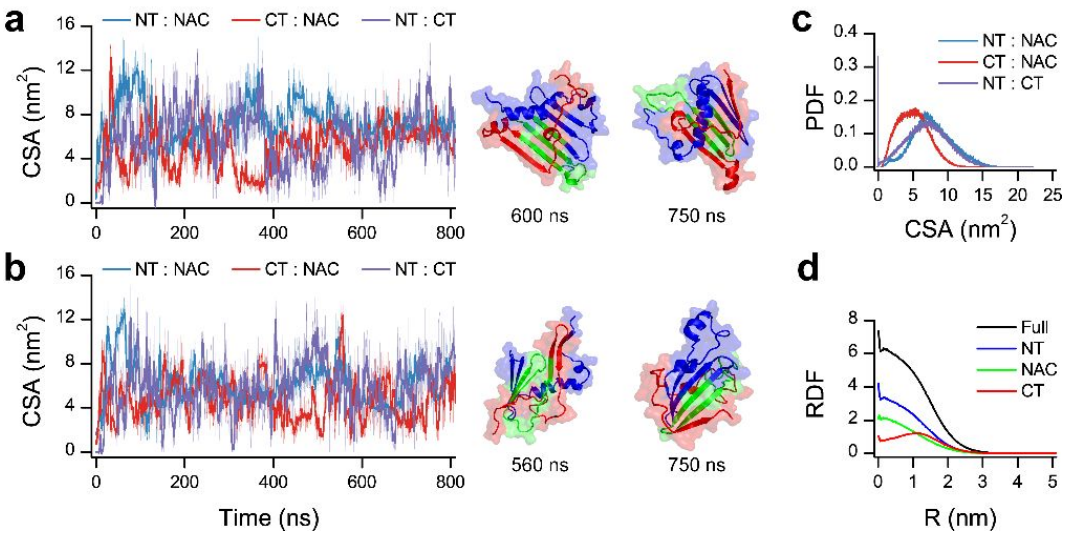

Figure S6. Contact surface area analysis. The time evolution of the contact surface areas between N-terminus and NAC region, between C-terminus and NAC region, and between N-terminus and C-termimus **a&b)**. Two represented trajectories are randomly selected from 100 independent DMD simulations. The probability distribution of the contact surface area between N-terminus and NAC region, between C-terminus and NAC region, and between N-terminus and C-terminus **c)**. The radius distribution function of the Cα atom from N-terminus, NAC region, and C-terminus in the α-synuclein monomer **d)**.

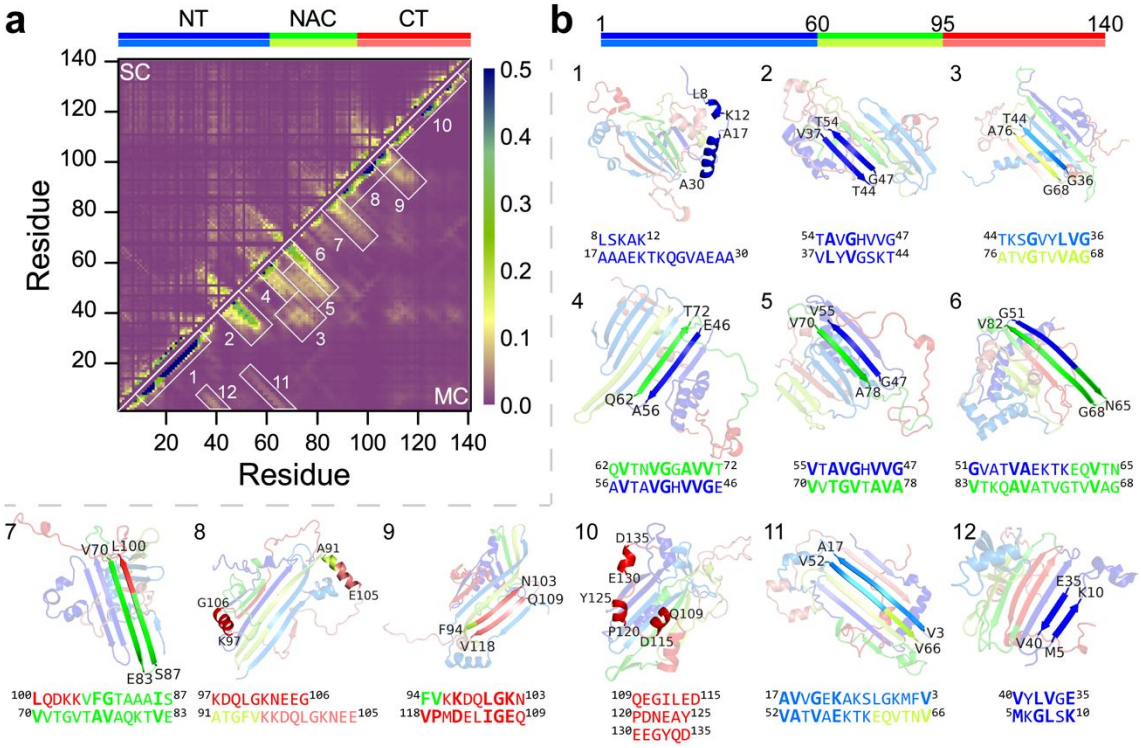

Figure S7. Intra-molecular residue-pairwise contact frequency of α-synuclein dimer. The intra-chain residue-pairwise contact frequency map of α-synuclein is computed both between main-chain atoms (MC-MC) and between side-chain atoms (SC-SC) based on the dimeric structures with number of inter-molecular contacts larger than 24 **a)**. The representative structured motifs with high contact frequency pattern, mostly corresponding to the helices or β-sheets, labeled as 1–12 in the contact frequency map are also presented **b).**

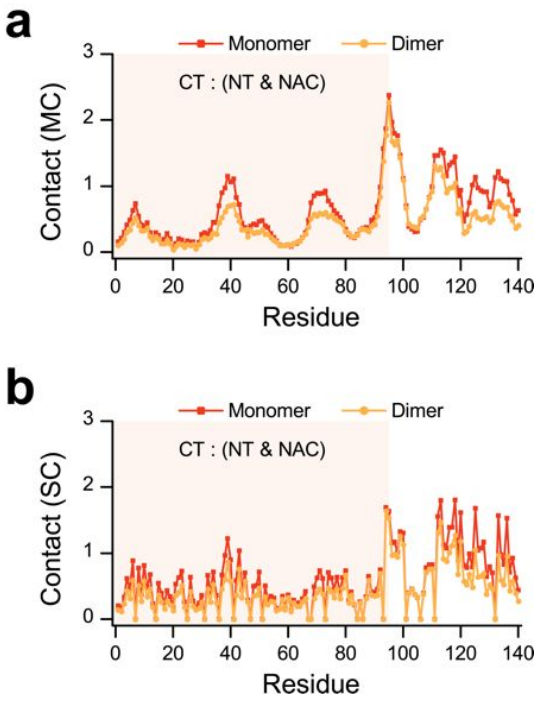

Figure S8. The interaction of C-terminus with N-terminus and NAC region analysis. The interaction of C-terminus with N-terminus and NAC region is examined by the average number of contacts of per residue formed by main-chain **a**) and side-chain **b**) atoms.