## **Supplementary Information:**

The Misfolding Mechanism of the Key Fragment R3 of Tau Protein: A Combined Molecular Dynamics Simulation and Markov State Model Study

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Replicas	Temperature (K)	Replicas	Temperature (K)
Replica-1	270.00	Replica-11	416.64
Replica-2	282.26	Replica-12	435.64
Replica-3	295.00	Replica-13	454.38
Replica-4	308.23	Replica-14	473.86
Replica-5	321.99	Replica-15	494.10
Replica-6	336.28	Replica-16	515.12
Replica-7	351.14	Replica-17	536.98
Replica-8	366.61	Replica-18	559.68
Replica-9	382.65	Replica-19	583.26
Replica-10	399.31	Replica-20	600.00

**Table S1.** Temperature (K) list used in the REMD simulation of 20 replicas of R3.



Figure S1. Replica traversal in the temperature space for the 20 replicas.



Figure S2. The validation of Markov state model. (A) Implied timescales as a function of the lag time. (B)-(D) are the Chapman-Kolmogorov test curves obtained by lumping 300 microstates into 15, 20, and 25 macrostates respectively. Where "i-i" represents the coincidence degree between the predicted probability of the MSM model and the simulation probability in ith macrostate. The first four macrostates were selected in the three C-K tests.