Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supplementary information

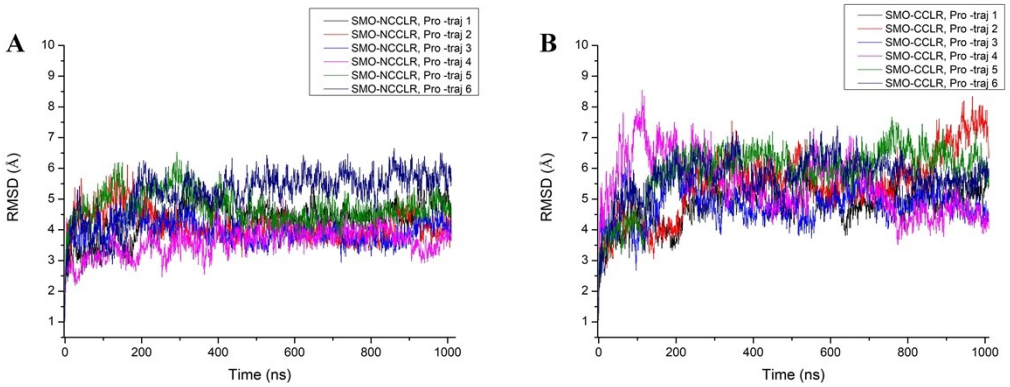

Fig. S1 The curves of RMSD based on the whole protein versus simulation time. (A) The RMSD curves of the whole protein of SMO-NCCLR system versus 1010 ns MD simulation time. (B) The RMSD curves of the whole protein of SMO-CCLR system versus 1010 ns MD simulation time. The different color curves represent different parallel trajectories.

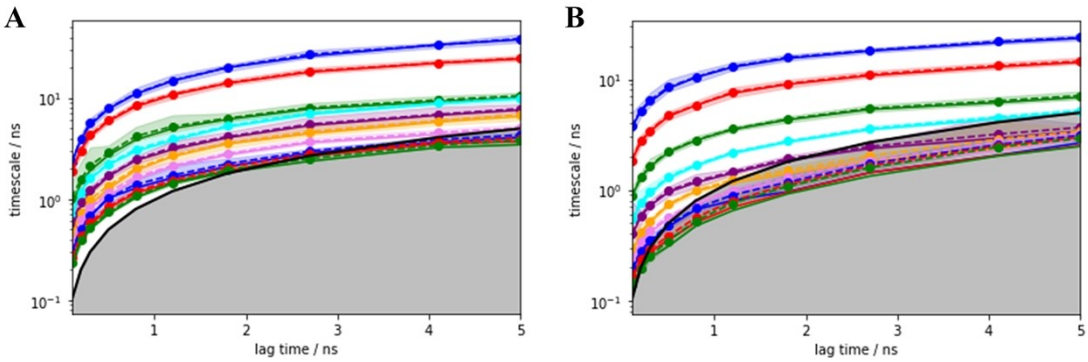

Fig. S2 The estimation of implied timescales (ITS) in different systems. (A) The ITS estimation to select the lag time in SMO-NCCLR. (B) The ITS estimation to select the lag time in SMO-CCLR.

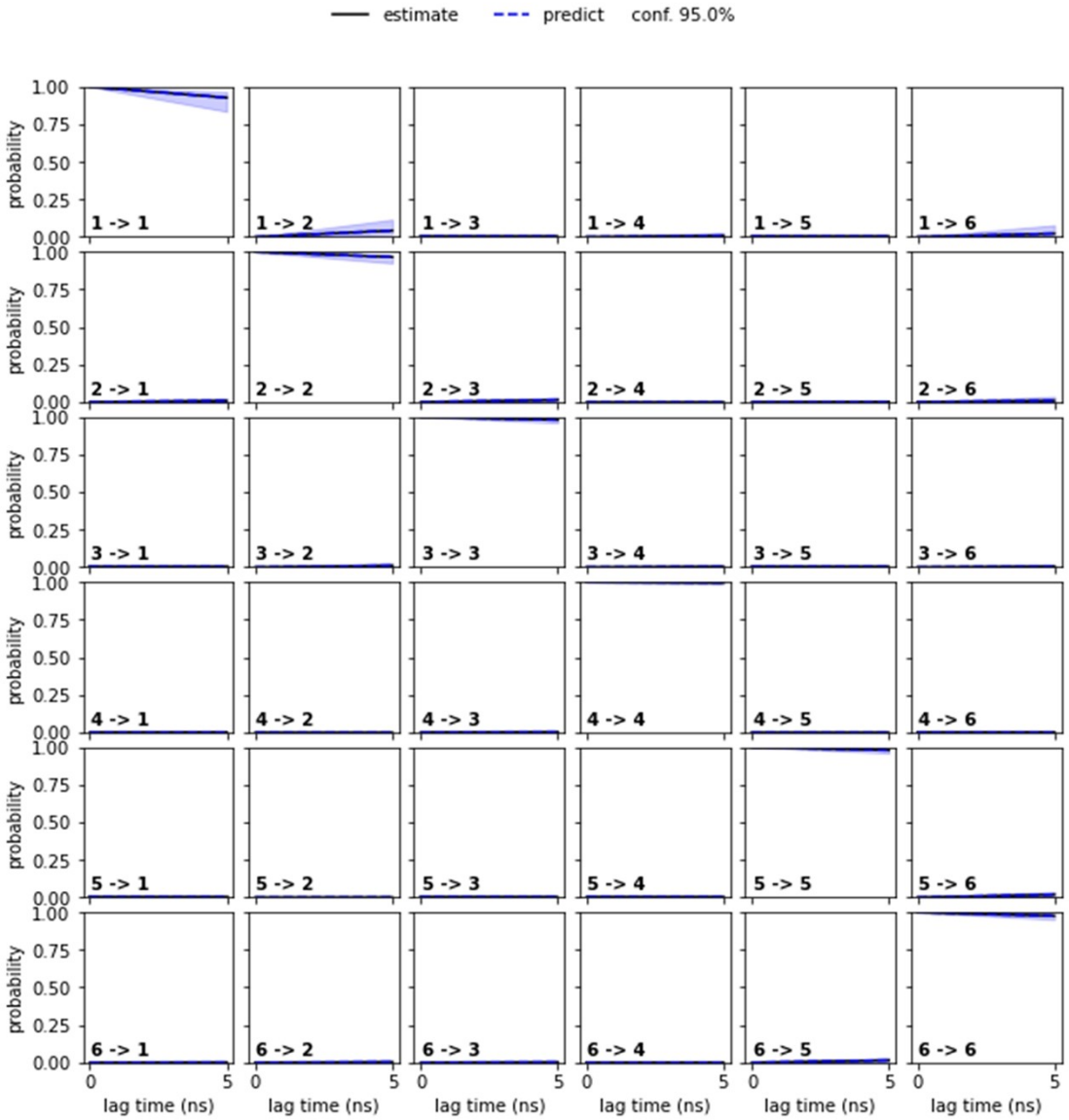

Fig. S3 Chapman-Kolmogorov test on the Bayesian Markov model at lag time 0.5 ns in SMO-NCCLR.

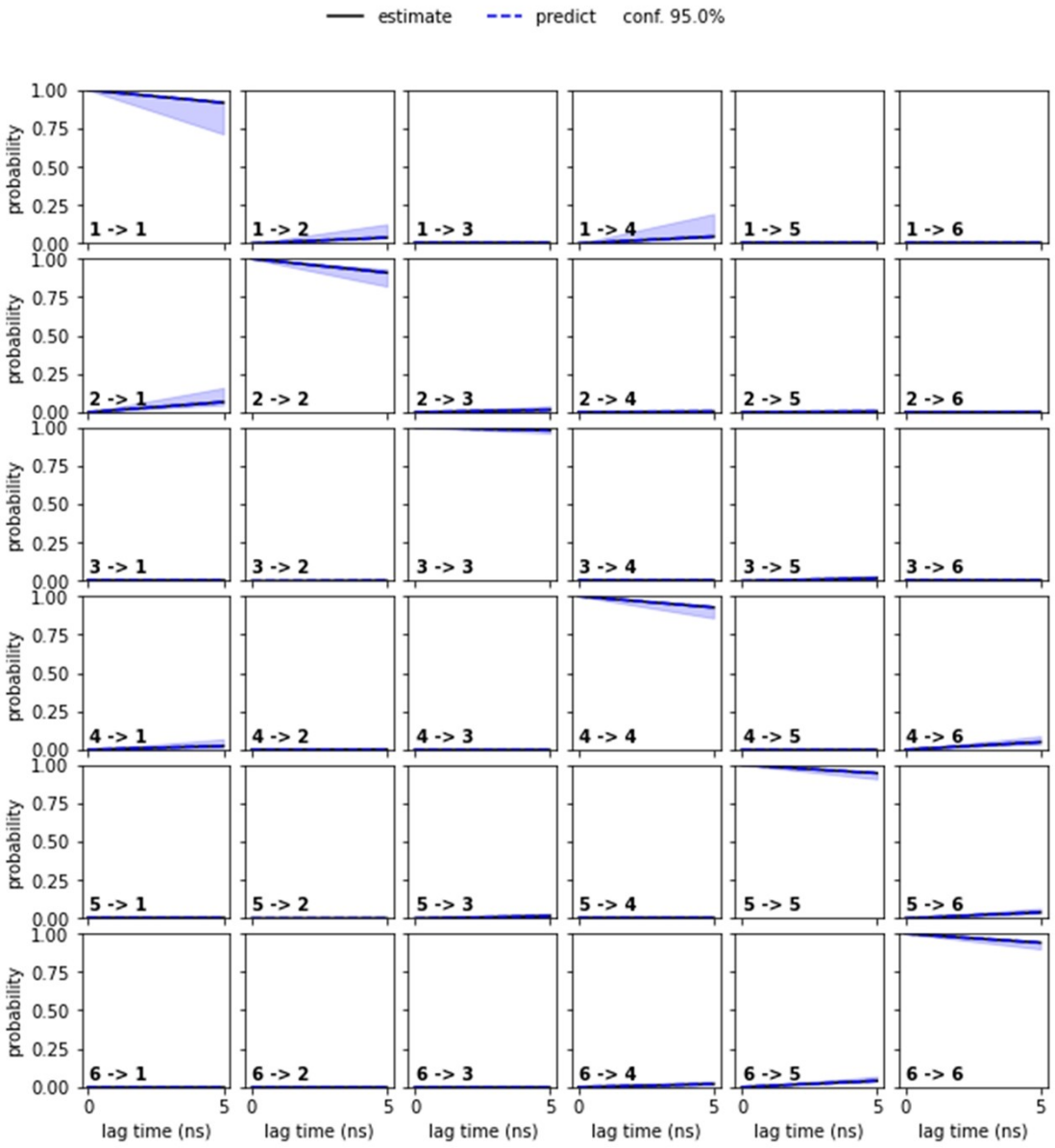

Fig. S4 Chapman-Kolmogorov test on the Bayesian Markov model at lag time 0.5 ns in SMO-CCLR.

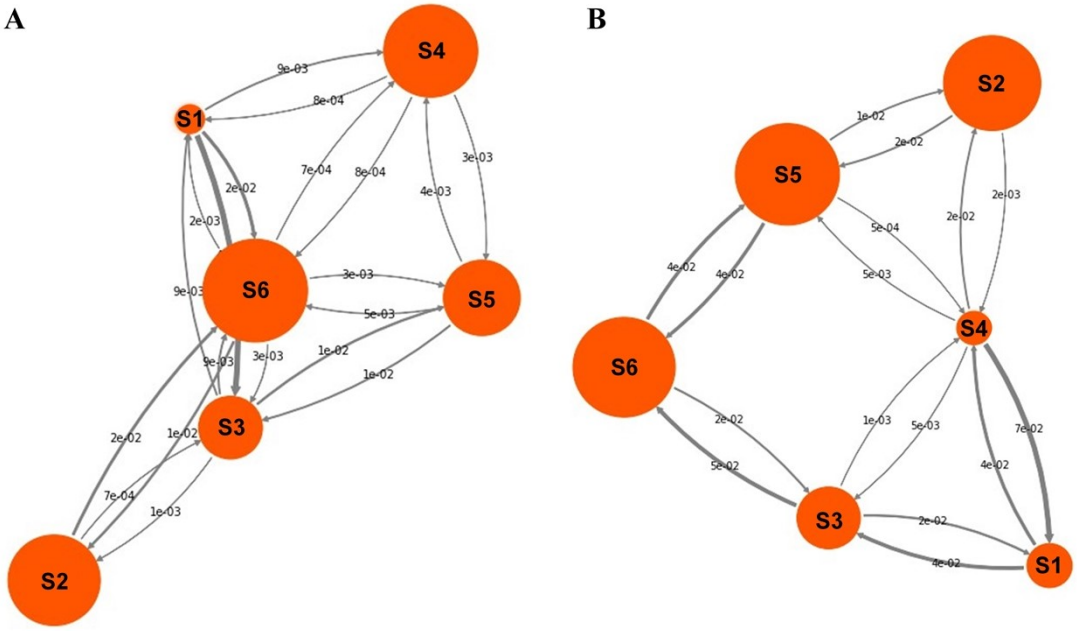

Fig. S5 The transition probability in different systems. (A) The transition probability in SMO-NCCLR. (B) The transition probability in SMO-CCLR. State 1-6 are abbreviated to S1-6. The size of each state is proportional to the life time of the corresponding state.

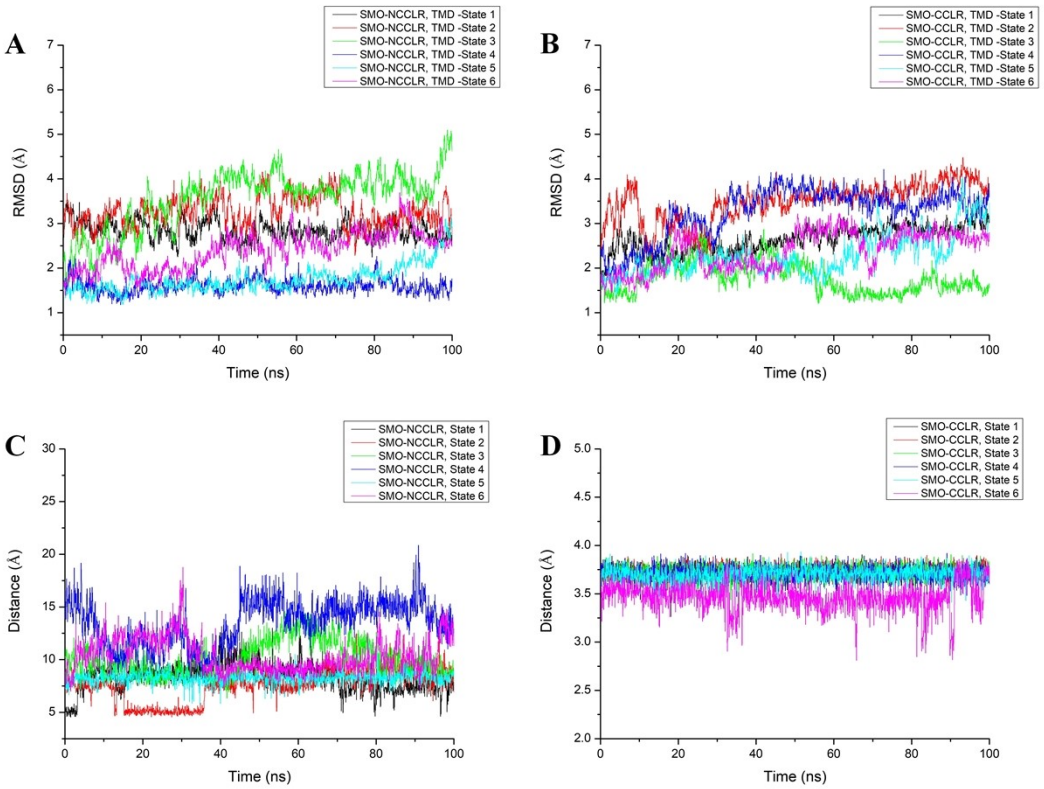

Fig. S6 The curves of TMD RMSD and distance versus simulation time. (A) TMD RMSD curves of representative structures of six states of SMO-NCCLR versus 100 ns MD simulation time. (B) TMD RMSD curves of representative structures of six states of SMO-CCLR versus 100 ns MD simulation time. (C) The distance between the Cα atoms of residue Asp95 and the oxygen atom on the 3β-hydroxyl group in cholesterol of representative structures of six states of SMO-NCCLR versus 100 ns MD simulation time. (D) The distance between the Cα atoms of residue Asp95 and the oxygen atom on the 3β-hydroxyl group in cholesterol of representative structures of six states of SMO-CCLR versus 100 ns MD simulation time. The different color curves represent different trajectories of representative structures of six states of different systems.

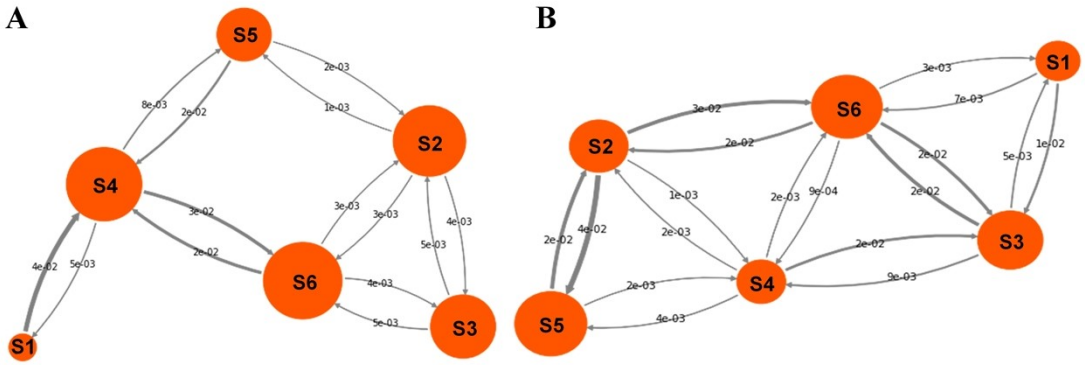

Fig. S7 The transition probability of six metastable states after MSM reconstruction in different systems. (A) The transition probability of six metastable states in SMO-NCCLR. (B) The transition probability of six metastable states in SMO-CCLR.

Table S1 Pathways induced from HMMs and flux of each pathway after MSM reconstruction in SMO-NCCLR

path	Path flux	% path	% of total
S1→S4→S6	0.00020288133148761654	97.5%	97.5%
S1→S4→S5→S2→S6	3.1663305227461353e-06	1.5%	99.0%
S1→S4→S5→S2→S3→S6	2.123574975409254e-06	1.0%	100.0%

Table S2 Pathways induced from HMMs and flux of each pathway after MSM reconstruction in SMO-CCLR

path	Path flux	% path	% of total
S1→S3→S6	0.000149966168760486	51.0%	51.0%
S1→S6	0.0001265098833599364	43.0%	94.1%
S1→S3→S4→S5→S2→S6	8.063993352033939e-06	2.7%	96.8%
S1→S3→S4→S6	5.02698705381631e-06	1.7%	98.5%
S1→S3→S4→S2→S6	4.336307732296836e-06	1.5%	100%