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

Use multiscale simulation to explore the effect of homo-dimerization between different conformation states on the activation and allosteric pathway for μ-opioid receptor

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Supporting information

Table S1. The averaged distances of TM3-TM6 (Å) over the last 10 μs trajectories of the 100 μs simulations for each parallel MD and their averaged values (labelled as Average) over the three parallel MDs.

	Average	Simulation 1	Simulation 2	Simulation 3
Inactive Monomer	12.6	12.2	14.3	11.4
Active Monomer	8.3	8.1	9.8	6.9
Protomer A of I-I dimer	14.1	13.7	16.1	12.4
Protomer B of I-I dimer	6.7	6.2	8.1	5.9
Inactive Protomer of A-I dimer	11.9	11.4	13.9	10.3
Active Protomer of A-I dimer	7.5	7.2	8.7	6.5

Table S2. The averaged distances of TM5-TM7 (Å) over the last 10 μs trajectories of the 100 μs simulations for each parallel MD and their averaged values (labelled as Average) over the three parallel MDs.

	Average	Simulation 1	Simulation 2	Simulation 3
Inactive Monomer	21.3	20.8	23.8	19.3
Active Monomer	21.0	20.8	23.1	19.0
Protomer A of I-I dimer	17.1	16.4	19.5	15.3
Protomer B of I-I dimer	19.2	18.4	22.3	16.8
Inactive Protomer of A-I dimer	8.4	8.1	9.7	7.4
Active Protomer of A-I dimer	13.4	12.7	14.1	13.5

Table S3. The averaged distances of TM3-TM7 (Å) over the last 10 μs trajectories of the 100 μs simulations for each parallel MD and their average values (labelled as Average) over the three parallel MDs.

	Average	Simulation 1	Simulation 2	Simulation 3
Inactive Monomer	16.2	15.9	17.7	15.1
Active Monomer	14.9	14.8	16.2	13.6
Protomer A of I-I diimer	7.9	7.5	9.8	6.3
Protomer B of I-I diimer	29.2	28.2	32.3	27.2
Inactive Protomer of A-I dimer	9.8	9.7	10.9	8.7
Active Protomer of A-I dimer	11.8	11.7	13.1	10.6

Table S4. The ΔRMSD values (Å) over the three parallel MD simulations for three key regions in each receptor unit of the four systems, derived from the last 10 μs equilibrium trajectories of 100 μs simulation [a].

		Simulation 1	Simulation 2	Simulation 3
Inactive Monomer	ECL2	-0.4	-1.1	-0.2
	ICL1-H8	-3.4	-4.0	-3.0
	NPxxY	-0.2	-1.1	-0.4
Active Monomer	ECL2	-0.1	-0.2	-0.3
	ICL1-H8	1.9	1.6	1.2
	NPxxY	0.3	0.2	0.2
Protomer A of I-I dimer	ECL2	-1.0	-2.3	-0.5
	ICL1-H8	0.5	0.1	0.7
	NPxxY	0.2	0.1	0.3
Protomer B of I-I dimer	ECL2	-1.4	-1.9	-1.1
	ICL1-H8	-2.1	-2.6	-1.8
	NPxxY	-1.3	-1.7	-1.1
Inactive protomer of A-I dimer	ECL2	-0.2	-0.4	-0.2
	ICL1-H8	-0.2	-0.5	-0.3
	NPxxY	0.9	1.2	0.8
Active protomer of A-I dimer	ECL2	0.6	0.4	0.7
	ICL1-H8	2.6	2.1	2.5
	NPxxY	0.9	1.0	1.2

[a] $\Delta RMSD = RMSD_{inactive} - RMSD_{active}$; $RMSD_{inactive}$ denote RMSD relative to the active crystal structure; $RMSD_{active}$ denote RMSD relative to the inactive crystal structure.

Table S5. The high correlated regions with the absolute values of correlation coefficients larger than 0.6 for the receptor in the four systems, derived from the last 100 ns trajectories of the three parallel all-atom MD simulations with 200 ns simulation times.

System	Simulation 1	Simulation 2	Simulation 3
Inactive Monomer	TM6-TM7	TM6-TM7 TM1-TM7	TM6-TM7
Active Monomer	TM5-TM6 TM3-TM6 TM4-TM5	TM5-TM6 TM3-TM6 TM4-TM5	TM5-TM6 TM3-TM6 TM4-TM5
Protomer A of I-I dimer	None	None	None
Protomer B of I-I dimer	TM2-TM3 TM3-TM4 TM2-TM4 TM3-TM5	TM2-TM3 TM4-TM5 TM3-TM5	TM2-TM3 TM3-TM4 TM2-TM4 TM3-TM5
Inactive protomer of A-I dimer	None	None	None
Active protomer of A-I dimer	TM3-TM5 TM1-TM7 TM2-TM7	TM3-TM5 TM1-TM7 TM2-TM7	TM3-TM5 TM1-TM7 TM2-TM7

Table S6. The highest frequency of the pathway from the ligand-binding pocket to the G-protein binding region for the three parallel MDs.

System	Simulation 1	Simulation 2	Simulation 3
Inactive Monomer	82.6%	70.1%	87.9%
Active Monomer	87.4%	78.0%	73.5%
Protomer A of I-I dimer	52.3%	41.6%	48.1%
Protomer B of I-I dimer	51.2%	42.6%	58.9%
Inactive protomer of A-I dimer	63.1%	58.3%	70.1%
Active protomer of A-I dimer	60.5%	65.8%	57.6%

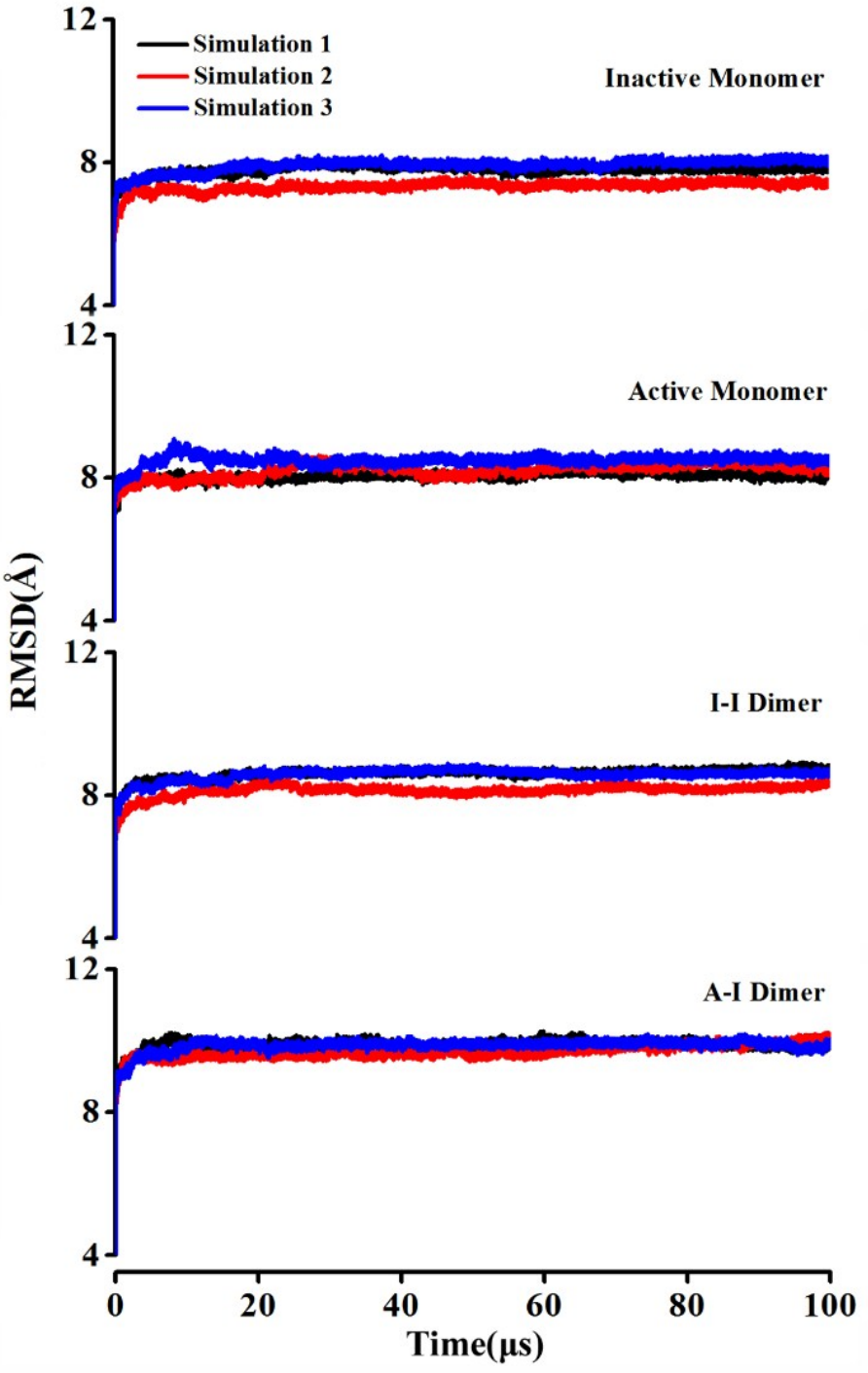

Figure S1. The RMSD values of backbone particles of the entire receptor system with respect to their initial structures for three parallel CGMD simulations.

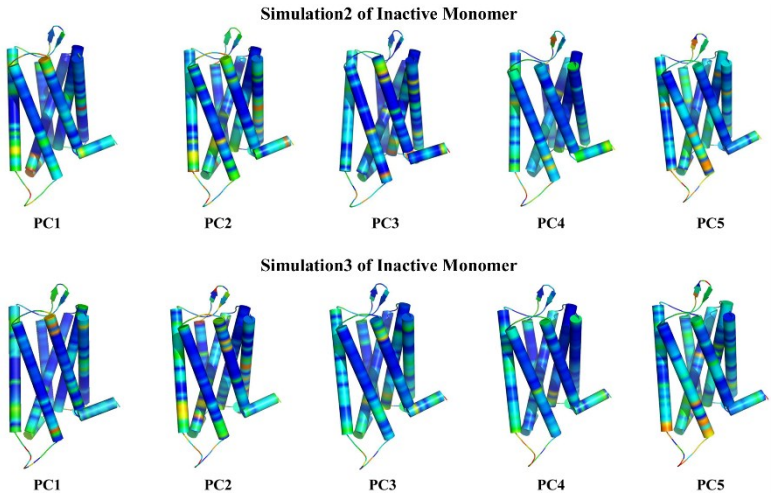

Figure S2. The projection of the first five eigenvectors for the other two parallel simulations (*e.g.*, simulation 2 and simulation 3) with the exception of simulation 1 in the text for the inactive monomer. The colours from red to blue correspond to the mobility from large to small.

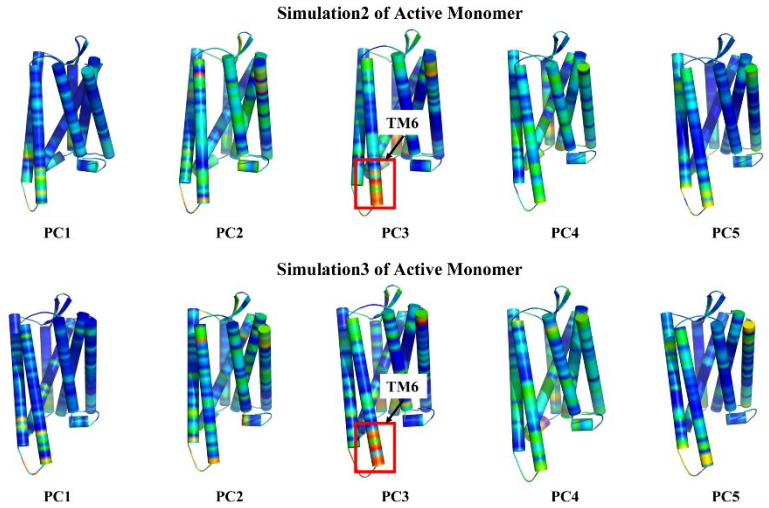

Figure S3. The projection of the first five eigenvectors for the other two parallel simulations (*e.g.*, simulation 2 and simulation 3) with the exception of simulation 1 in text for the active monomer. The colours from red to blue correspond to the mobility from large to small.

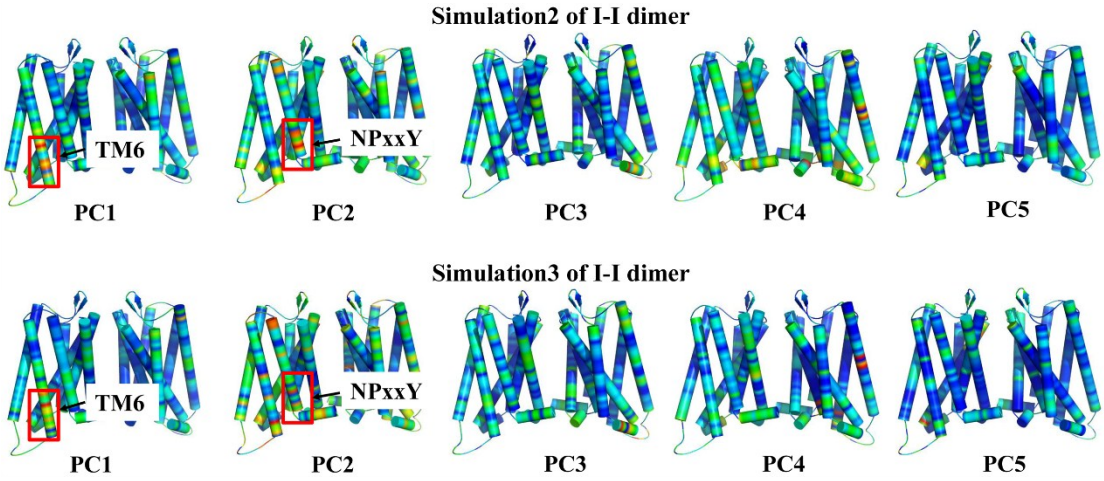

Figure S4. The projection of the first five eigenvectors for the other two parallel simulations (*e.g.*, simulation 2 and simulation 3) of the I-I dimer. The colors from red to blue correspond to the mobility from large to small.

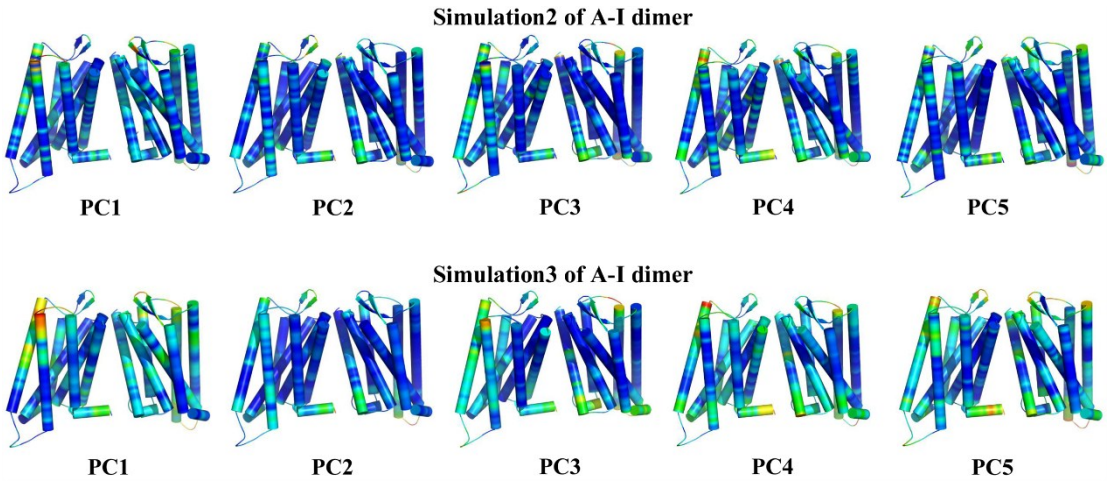

Figure S5. The projection of the first five eigenvectors for the other two parallel simulations (*e.g.*, simulation 2 and simulation 3) with the exception of simulation 1 in text for the A-I dimer. The colors from red to blue correspond to the mobility from large to small.