Supporting Information

Key Residues in δ Opioid Receptor Allostery Explored by the Elastic Network Model and the Complex Network Model Combined with the Perturbation Method

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Table S1. Average PCC value (PCC_{AVE}) of PCC_{MSF} and PCC_{CoF} indicating the PCC values between the predicted residue MSFs and CoFs by $fcfGNM_{MD}$/GNM under the optimized parameters (listed in the last two columns) and the corresponding values from the MD ensemble respectively for δ opioid receptor (DOP).

Method	PCC_{AVE}	PCC_{MSF}	PCC_{CoF}	r_c (Å)	ρ
MD trajectory 10713					
$fcfGNM_{MD}$	0.78	0.87	0.69	10	10^{-1}
GNM	0.70	0.82	0.58	8	
MD trajectory 10714					
$fcfGNM_{MD}$	0.85	0.93	0.77	13	10^{-2}
GNM	0.67	0.80	0.54	8	
MD trajectory 10715					
$fcfGNM_{MD}$	0.78	0.89	0.67	13	1
GNM	0.72	0.84	0.60	7	
On average					
$fcfGNM_{MD}$	0.80±0.04	0.90±0.03	0.71±0.05		
GNM	0.70±0.03	0.82±0.02	0.57±0.03		

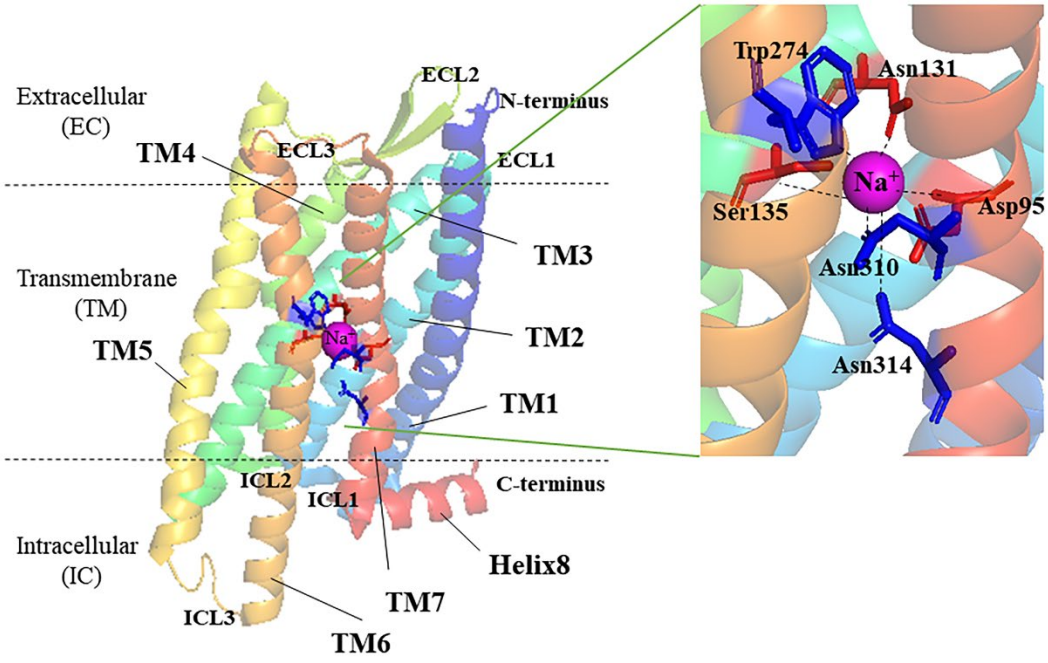

Figure S1. Crystal structure of δ opioid receptor (DOP) whose PDB ID is 4N6H. The seven transmembrane helixes (TM1-7) are indicated in different colors, which are connected by three extracellular loops (ECL1-3) and three intracellular loops (ICL1-3). The sodium ion is shown as a purple sphere and the residues in the first and second sodium coordination shells shown as red and blue sticks respectively.

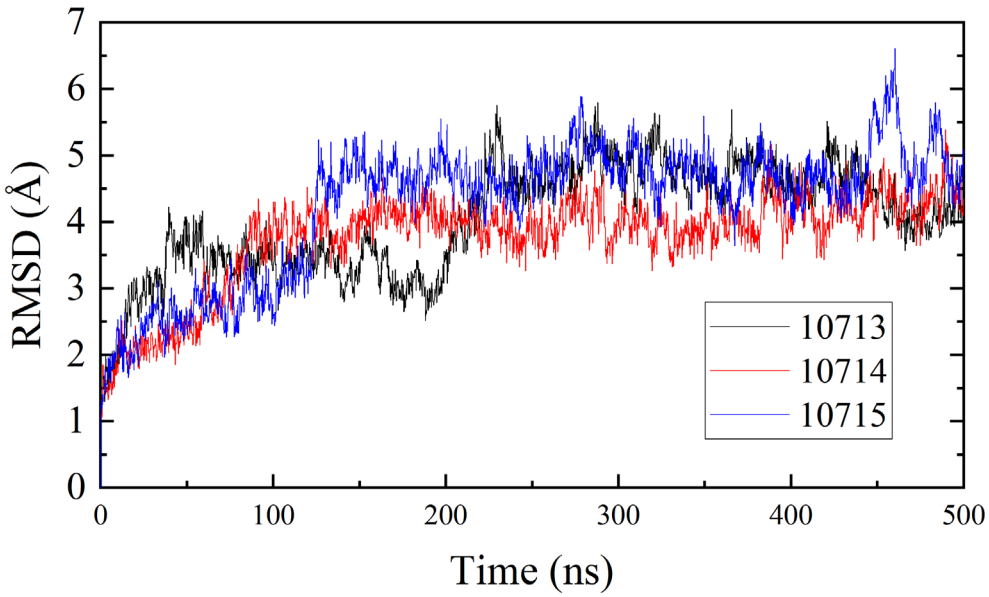

Figure S2. Time evolutions of root mean square deviation (RMSD) of backbone atoms of DOP during its three 500 ns MD simulations.

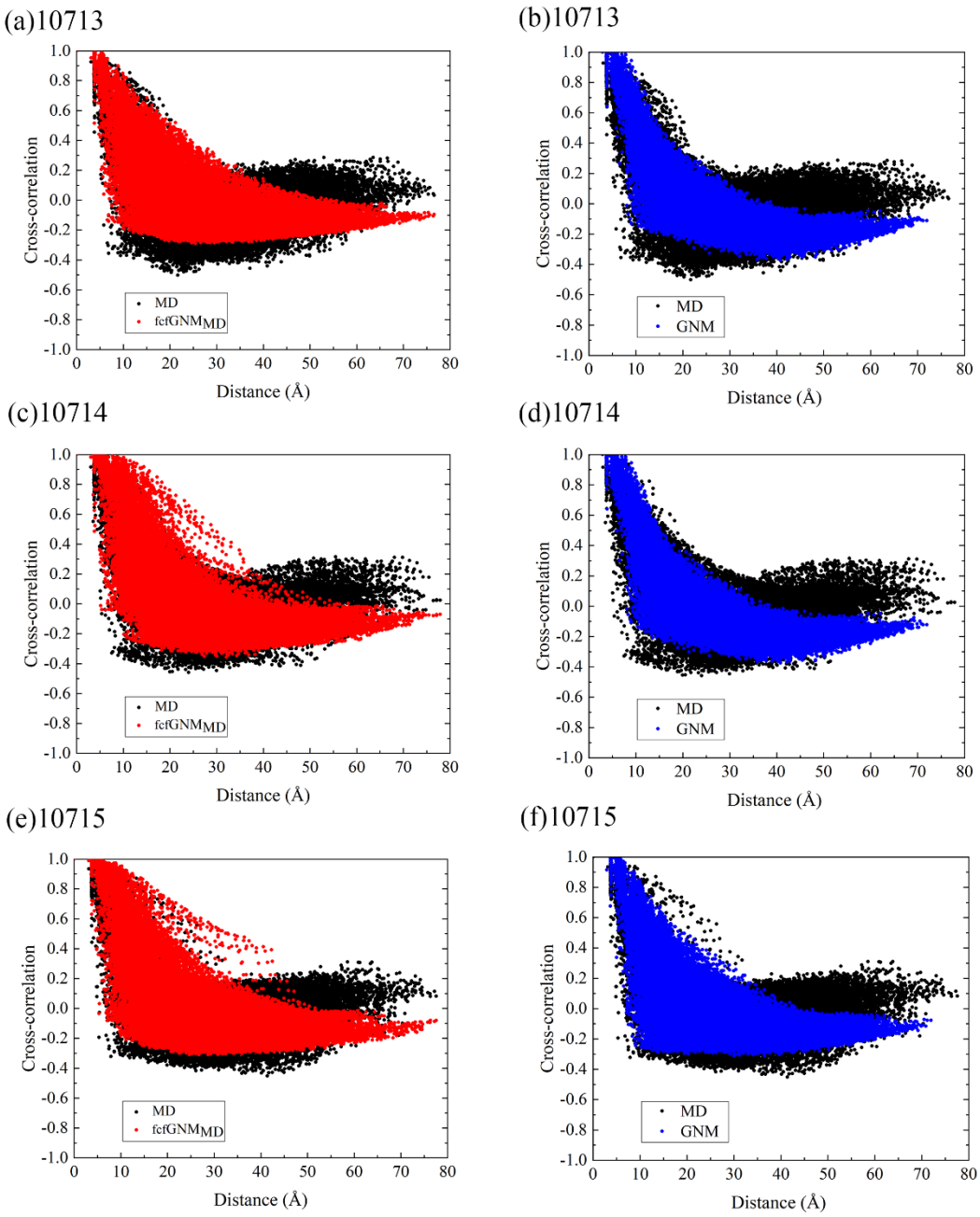

Figure S3. Distributions of dynamic cross-correlations concerning the inter-residue distance for DOP obtained from $fcfGNM_{MD}$ (a, c, e) and traditional GNM (b, d, f) at the best PCC_{DCCM} values respectively, with the corresponding results from MD ensembles also shown for comparison.

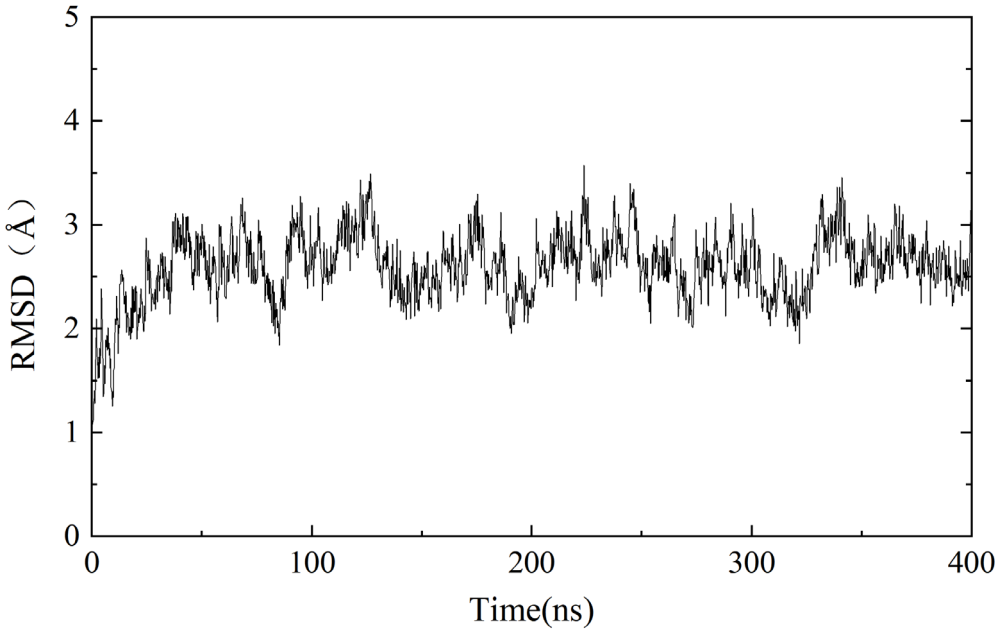

Figure S4. Time evolution of RMSD of backbone atoms in DOP complex with naltrindole during MD simulation (from GPCRmd database).

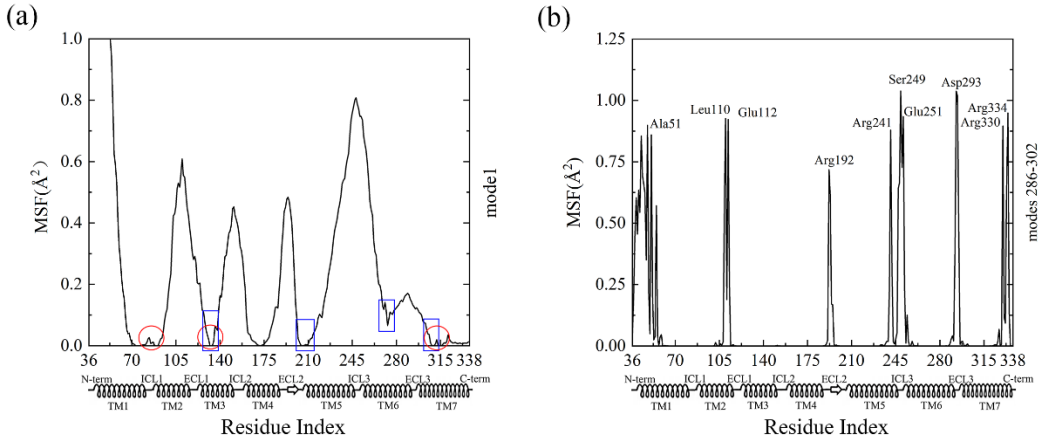

Figure S5. For the DOP complex with naltrindole, the residue MSF profiles from the slowest mode (a) and from the sixteen fastest modes (b) obtained by fcfDNM$_{MD}$. The fcfGNM$_{MD}$ model achieves the highest PCC_{AVE} of 0.87 when adopting a set of optimal parameters with ρ = 1 and r_c = 12 Å. The regions with minimum mobilities in (a) are labeled with red circles (sodium binding pocket) and blue rectangles (ligand binding sites), and the active residues in (b) are labeled with residue numbers.

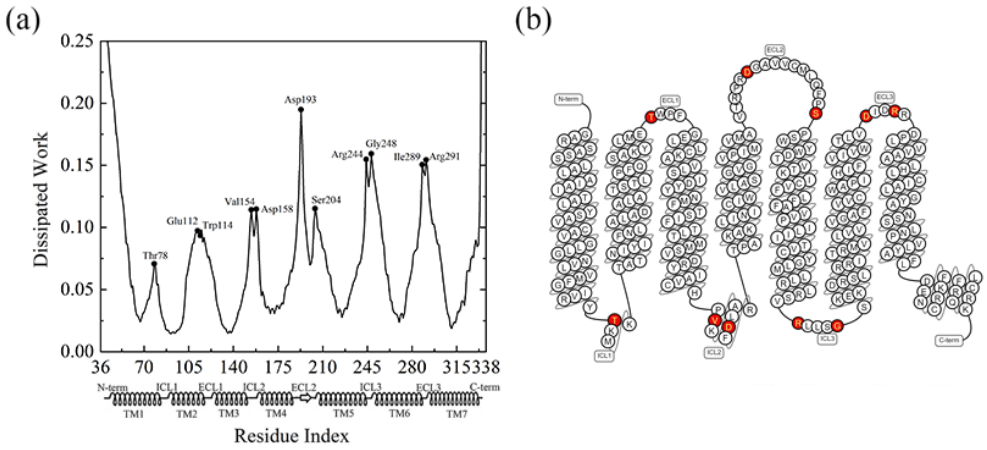

Figure S6. Dissipated work as a function of residue index caused by a periodic force with $\xi\omega = \lambda_2$ (the second eigenvalue from fcfGNM$_{MD}$ corresponding to the lowest frequency) in the structure of DOP (a) and DOP's topology with the peaks in the dissipated work curve highlighted by red color (b).

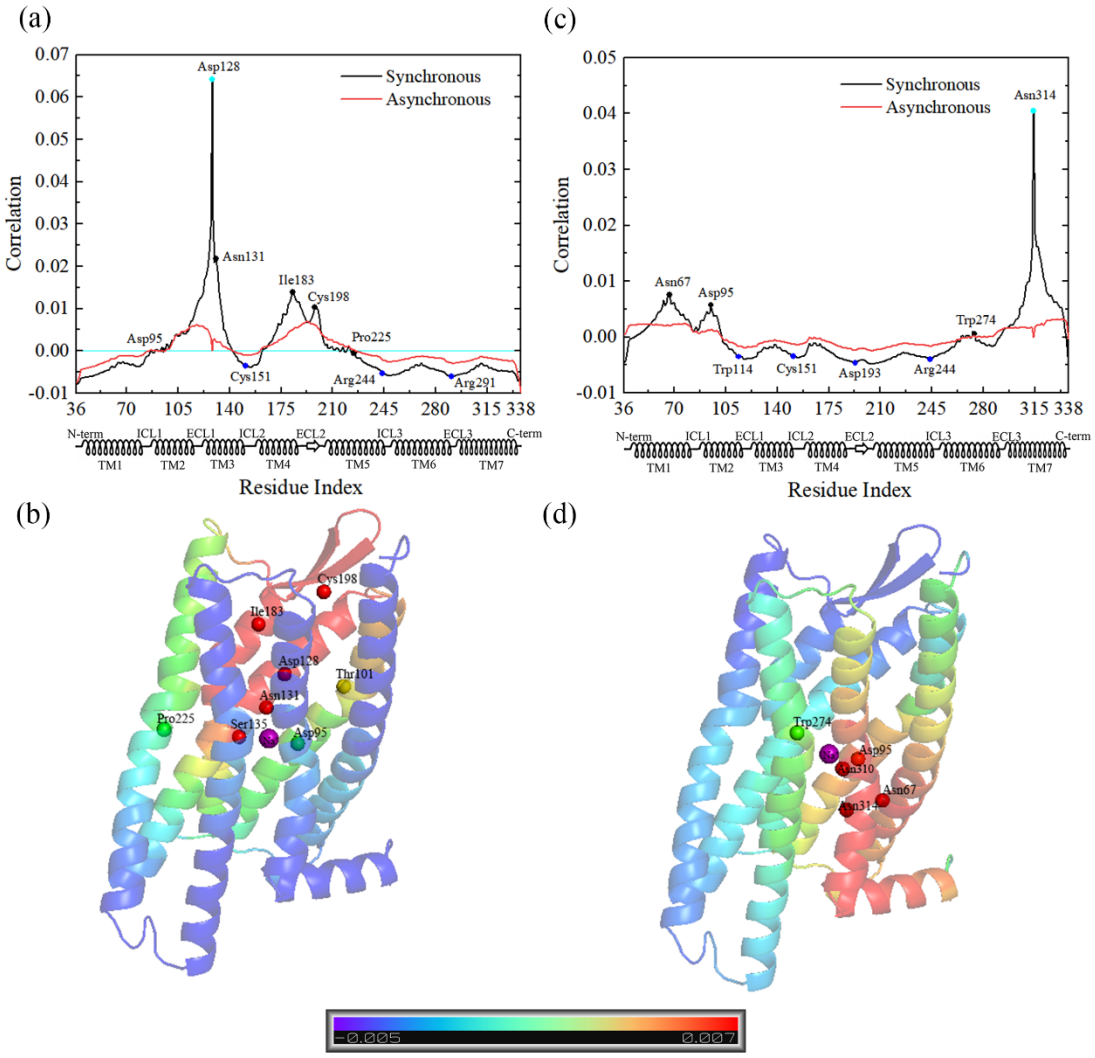

Figure S7. Residue correlations caused by the periodic perturbations on residues Asp128 (a) and Asn314 (c), and DOP structures color-coded by the corresponding synchronous components shown in (b) and (d) respectively. The residues evidently coupled to the perturbed residues are highlighted by the spheres colored according to the correlation level with the sodium ion shown as a purple sphere.

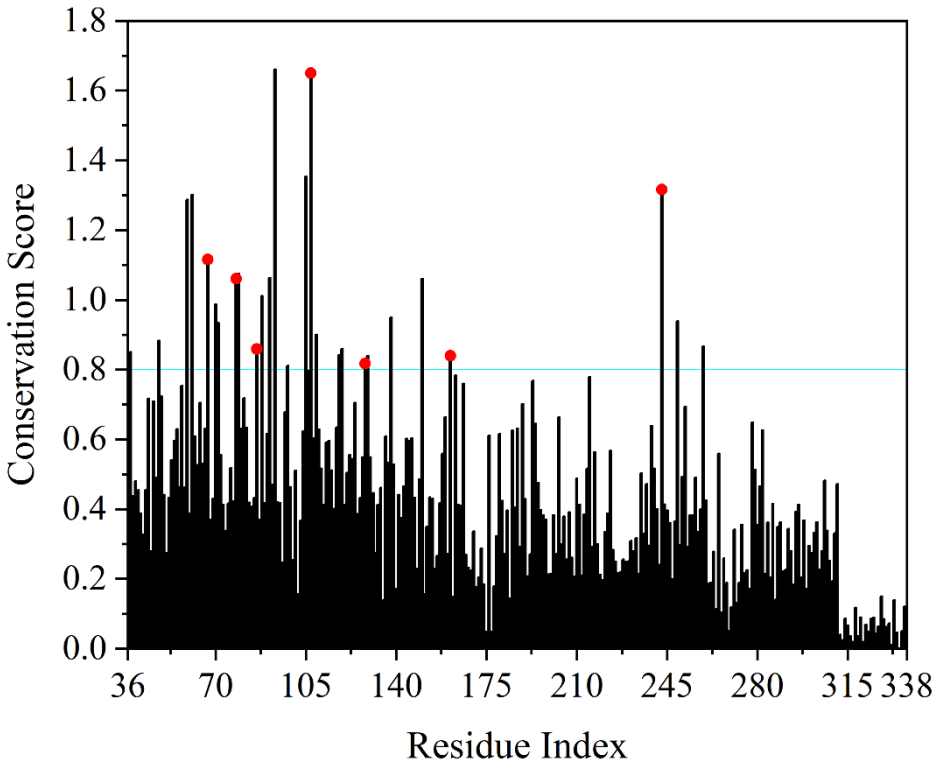

Figure S8. Residue conservation from a multiple sequence alignment of 1000 GPCR sequences (which were collected through blastp search in the non-redundant protein sequence database with default parameters. Based on the sequences, the residue conservation analysis was performed by MISTIC approach), with the residue index corresponding to the reference structure 4n6h. The identified key residues Asn67$^{1.50}$, Thr78^{ICL1}, Ile86$^{2.41}$, Ala107$^{2.62}$, Asp128$^{3.32}$, Thr161$^{4.38}$, and Val243$^{5.68}$ (marked in red) in this work are of relative high conservation.