Supporting Information

Accurate Free Energy Estimator: Based on MM/PBSA Combined with Interaction Entropy for Protein–Ligand Binding Affinity

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Table Captions

Table S1 The PDBID and protein name of training set and test set.

Data Set	PDBID	Protein Name
training set	1PU8	3-Methyladenine Dna Glycosylase
training set	1ACJ	Acetylcholinesterase
training set	1U0H	Adenylate Cyclase, Type V
test set	1WS5	Agglutinin Alpha Chain
training set	1F2O	Aminopeptidase
training set	1T7F	Androgen Receptor
test set	2HVC	
training set	1CZE	Aspartate Aminotransferase
	1FJ4	Beta-Ketoacyl-[Acyl Carrier Protein] Synthase I
	1LQD	Blood Coagulation Factor Xa
test set	1XH6	Camp-Dependent Protein Kinase, Alpha-Catalytic Subunit
test set	1XLZ	Camp-Specific 3',5'-Cyclic Phosphodiesterase 4B
test set	1Y2B	Camp-Specific 3',5'-Cyclic Phosphodiesterase 4D
	1Y2D	
	1Y2E	
	1ZKN	
test set	1ZKL	High-Affinity Camp-Specific 3',5'-Cyclic Phosphodiesterase 7A
training set	1Q9M	Camp-Specific Phosphodiesterase Pde4D2
training set	1AYU	Cathepsin K
	1Q6K	
training set	1MS6	Cathepsin S
	1NPZ	
	1NQC	
training set	1OGU	Cell Division Protein Kinase 2
test set	2C5N	
	2C5O	
training set	1R6Z	Chimera Of Maltose-Binding Periplasmic Protein And Argonaute 2
test set	2H44	
test set	2H96	C-Jun-Amino-Terminal Kinase-Interacting Protein 1
training set	1BIO	Complement Factor D
training set	1ME3	Cruzipain
	1ME4	
training set	1FVV	Cyclin-Dependent Kinase 2
training set	1SQB	Cytochrome B
	1SQP	
	1SQQ	
training set	1KMV	Dihydrofolate Reductase
training set	1RRW	Dihydroneopterin Aldolase

training set	1E34	Elastase
training set	1QI0	Endoglucanase B
training set	1ENT	Endothiapepsin
training set	1CR6	Epoxide Hydrolase
training set	1ETS	Epsilon-Thrombin
training set	1G50	Estrogen Receptor
	1PCG	
	1QKU	
test set	1ZKY	
	2B1V	
	2FAI	
test set	1X7E	Estrogen Receptor 1 (Alpha)
training set	1U3Q	Estrogen Receptor Beta
	1U3R	
	1U3S	
test set	1X7B	
training set	1B56	Fatty Acid Binding Protein
training set	1TR7	Fimh Protein
test set	2ETM	Focal Adhesion Kinase 1
training set	1OFZ	Fucose-Specific Lectin
test set	2FDD	Gag-Pol Polyprotein
training set	1K3T	Glyceraldehyde-3-Phosphate Dehydrogenase
training set	1Q41	Glycogen Synthase Kinase-3 Beta
training set	1LT5	Heat-Labile Enterotoxin
training set	1HIV	Hiv-1 Protease
	1MEU	
	1ODY	
test set	1VRT	Hiv-1 Reverse Transcriptase
test set	2B1Q	Hypothetical Protein Slr0953
	2D2V	
training set	1D6N	Protein (Hypoxanthine-Guanine Phosphoribosyltransferase)
test set	1FSG	Hypoxanthine-Guanine Phosphoribosyltransferase
training set	1DBB	Igg1-Kappa Db3 Fab (Light Chain)
	1DBK	
training set	1Q0B	Kinesin-Like Protein Kif11
training set	1LFO	Liver Fatty Acid Binding Protein
training set	1LJT	Macrophage Migration Inhibitory Factor
test set	2GH9	Maltose/Maltodextrin-Binding Protein
training set	1N3W	Maltose-Binding Periplasmic Protein
	1RM8	Matrix Metalloproteinase-16
test set	2AA6	Mineralocorticoid Receptor
test set	1TVO	Mitogen-Activated Protein Kinase 1
	1WZY	

test set	1W7H	Mitogen-Activated Protein Kinase 14
	1W84	
	1WBW	
test set	1K03	Nadph Dehydrogenase 1
test set	2A4G	Ns3 Protease/Helicase
training set	1E00	Odorant-Binding Protein
	1HN2	
training set	1DI9	P38 Kinase
training set	1RIN	Pea Lectin
training set	1H60	Pentaerythritol Tetranitrate Reductase
	1H61	
test set	2G0G	Peroxisome Proliferator-Activated Receptor Gamma
training set	1LF3	Plasmepsin 2
training set	1NPV	Pol Polyprotein
test set	1Z1R	
training set	1G27	Polypeptide Deformylase
	1G2A	
test set	2AI8	
training set	1SQN	Progesterone Receptor
test set	2BBB	Protease
training set	1B4D	Protein （Glycogen Phosphorylase B）
	1C85	Protein (Protein-Tyrosine Phosphatase 1B)
test set	2CM7	Tyrosine-Protein Phosphatase Non-Receptor Type 1
	2CNF	
training set	1F0Q	Protein Kinase Ck2, Alpha Subunt
test set	2A2G	Protein(Alpha-2U-Globulin)
training set	1FBM	Protein(Cartilage Oligomeric Matrix Protein)
training set	1O4J	Proto-Oncogene Tyrosine-Protein Kinase Src
training set	1I80	Purine Nucleoside Phosphorylase
	1PWY	
test set	1V2H	
	1V41	
training set	1N2V	Queuine Trna-Ribosyltransferase
training set	1BIL	Renin
	1HRN	
test set	2G1R	
	2G24	
training set	1IL3	Ricin A Chain
	1IL4	
	1IL9	
test set	2E9N	Serine/Threonine-Protein Kinase Chk1
training set	1C3I	Stromelysin-1
	1G4K	

test set	2D06	Sulfotransferase 1A1
training set	1PY5	Tgf-Beta Receptor Type I
test set	1VJY	
training set	1D1P	Tyrosine Phosphatase

Table S2. The energy terms of binding free energy and SEM on the training set. All values are kcal/mol.

No.	PDBID	MM/PBSA				$-T\Delta S_{IE}$
		ΔE_{ele}	ΔE_{vdW}	ΔG_{np}	ΔG_{pb}	
1	1ACJ	-9.07±0.18	-30.24±0.15	-4.05±0.02	38.07±0.28	4.52±0.00
2	1AYU	-55.06±0.47	-53.46±0.33	-6.55±0.02	75.16±0.50	14.57±0.00
3	1B4D	-106.27±0.67	-27.99±0.44	-4.36±0.01	105.95±0.44	18.94±0.01
4	1BIO	-29.74±0.45	-20.77±0.20	-3.10±0.01	43.80±0.49	13.06±0.01
5	1B56	-188.44±0.66	-38.13±0.28	-5.45±0.01	167.72±0.61	24.61±0.01
6	1BIL	-68.27±0.44	-74.16±0.42	-8.69±0.01	89.55±0.38	13.55±0.00
7	1C3I	-208.23±0.78	-50.29±0.25	-5.94±0.01	237.79±0.63	23.45±0.01
8	1C85	-133.89±0.98	-22.68±0.33	-3.39±0.01	127.88±0.75	25.67±0.01
9	1CR6	-8.41±0.25	-43.52±0.20	-5.21±0.01	38.14±0.31	9.38±0.01
10	1CZE	-207.97±1.60	-6.14±0.33	-2.77±0.01	175.65±1.24	38.85±0.02
11	1D1P	-130.94±1.00	-25.91±0.24	-3.46±0.01	123.46±0.82	27.52±0.01
12	1DBB	-19.16±0.29	-47.40±0.24	-4.78±0.01	32.37±0.18	9.47±0.00
13	1DBK	-12.49±0.24	-39.21±0.28	-4.41±0.01	25.47±0.24	7.83±0.00
14	1DI9	-13.87±0.28	-41.10±0.25	-5.06±0.01	29.72±0.27	8.46±0.01
15	1D6N	-21.51±0.29	-20.66±0.21	-2.91±0.00	36.58±0.26	5.55±0.00
16	1E00	-3.34±0.13	-29.39±0.17	-4.04±0.01	17.05±0.19	4.38±0.00
17	1E34	-106.89±0.76	-34.82±0.25	-4.33±0.01	114.42±0.61	26.48±0.03
18	1ENT	-64.96±0.58	-61.67±0.32	-7.77±0.02	97.82±0.53	18.84±0.00
19	1ETS	-28.75±0.99	-54.71±0.37	-6.39±0.01	27.58±0.75	35.29±0.01
20	1F0Q	-35.68±0.51	-35.74±0.27	-4.10±0.01	47.75±0.34	15.45±0.00
21	1F2O	-55.52±0.57	-16.29±0.32	-3.18±0.01	52.42±0.42	12.82±0.00
22	1FBM	-6.61±0.16	-44.27±0.21	-5.73±0.01	23.51±0.23	6.46±0.00
23	1FJ4	-7.38±0.19	-36.05±0.22	-4.04±0.01	29.71±0.29	5.39±0.00
24	1FSG	-43.62±0.45	-23.04±0.21	-3.04±0.00	35.15±0.21	13.72±0.01
25	1FVV	-35.51±0.57	-53.50±0.27	-5.87±0.02	67.14±0.42	14.94±0.01
26	1G27	-51.90±0.55	-35.44±0.35	-4.88±0.01	53.96±0.36	12.77±0.01
27	1G2A	-59.37±1.05	-43.46±0.41	-5.33±0.01	65.93±0.76	25.54±0.03
28	1G4K	-19.73±0.39	-40.51±0.26	-4.81±0.01	38.91±0.38	11.25±0.01
29	1G50	-27.70±0.45	-41.30±0.26	-4.64±0.01	37.21±0.21	14.31±0.01
30	1HN2	-5.85±0.13	-31.95±0.17	-3.86±0.01	19.43±0.18	4.25±0.00
31	1H60	-13.07±0.22	-31.24±0.20	-4.36±0.01	27.82±0.45	10.24±0.01
32	1H61	-14.56±0.41	-37.36±0.22	-5.07±0.01	40.16±0.38	10.91±0.01
33	1HIV	-82.41±0.65	-88.76±0.45	-9.46±0.02	112.96±0.49	21.53±0.01
34	1HRN	-47.87±0.71	-63.43±0.36	-7.41±0.01	77.28±0.54	29.09±0.01
35	1I80	-39.57±0.32	-20.49±0.23	-2.91±0.01	42.46±0.34	6.99±0.00
36	1IL3	-33.14±0.33	-25.80±0.22	-2.96±0.00	38.50±0.18	9.71±0.00
37	1IL4	-34.15±0.37	-25.94±0.21	-2.97±0.00	39.78±0.20	9.23±0.00
38	1IL9	-31.96±0.45	-27.84±0.23	-3.17±0.00	35.98±0.27	9.70±0.00

39	1K03	-28.08±0.26	-19.93±0.20	-2.97±0.01	38.83±0.22	5.94±0.00
40	1K3T	-8.32±0.30	-27.53±0.20	-4.15±0.01	20.24±0.31	8.64±0.00
41	1KMV	-7.76±0.35	-44.61±0.22	-5.45±0.01	34.06±0.62	11.21±0.00
42	1LF3	-63.20±0.56	-78.93±0.42	-9.38±0.03	95.24±0.55	19.11±0.00
43	1LFO	-200.51±0.91	-40.98±0.36	-6.33±0.01	208.44±0.70	25.02±0.01
44	1LJT	-42.49±0.41	-34.15±0.25	-4.13±0.01	52.49±0.34	10.82±0.01
45	1LQD	20.69±0.56	-50.11±0.32	-5.72±0.02	7.89±0.43	19.60±0.01
46	1LT5	-59.76±0.82	-29.59±0.34	-4.36±0.02	65.24±0.61	24.01±0.02
47	1ME3	-34.31±0.57	-49.59±0.27	-5.66±0.01	53.65±0.46	17.06±0.01
48	1ME4	-50.30±0.61	-45.30±0.30	-5.64±0.02	61.24±0.44	20.85±0.01
49	1MEU	-48.16±0.57	-34.49±0.39	-5.62±0.01	62.73±0.44	15.59±0.02
50	1MS6	-23.50±0.41	-44.37±0.25	-5.05±0.02	38.78±0.29	10.39±0.01
51	1N2V	-52.23±0.43	-31.36±0.29	-3.72±0.01	54.20±0.46	13.46±0.00
52	1N3W	-140.96±0.78	-27.82±0.51	-4.75±0.01	131.27±0.45	19.40±0.00
53	1NPV	-66.35±0.43	-80.23±0.32	-7.85±0.01	109.33±0.41	15.26±0.00
54	1NPZ	-23.19±0.44	-52.03±0.30	-6.08±0.02	47.95±0.33	10.68±0.00
55	1NQC	-20.12±0.41	-43.68±0.34	-5.54±0.02	40.08±0.34	11.24±0.01
56	1O4J	-17.71±0.43	-12.80±0.20	-2.95±0.01	29.25±0.54	10.22±0.00
57	1ODY	-62.68±0.55	-69.15±0.36	-9.13±0.02	99.42±0.82	20.27±0.01
58	1OFZ	-55.69±0.79	-14.20±0.28	-2.91±0.01	48.48±0.63	17.89±0.01
59	1OGU	-40.69±0.44	-50.57±0.25	-5.49±0.01	59.42±0.37	10.65±0.01
60	1PCG	-21.61±0.31	-39.16±0.26	-4.73±0.01	35.77±0.21	7.07±0.00
61	1PU8	-40.18±0.38	-22.83±0.16	-3.25±0.01	51.95±0.33	9.24±0.00
62	1PWY	-57.38±0.46	-33.88±0.25	-4.05±0.01	73.22±0.46	13.78±0.01
63	1PY5	-33.40±0.34	-42.57±0.26	-4.53±0.01	44.74±0.21	11.09±0.00
64	1Q0B	-26.57±0.24	-36.82±0.22	-4.39±0.01	38.67±0.16	6.22±0.00
65	1QKU	-30.08±0.32	-41.77±0.26	-4.66±0.01	41.08±0.19	7.98±0.01
66	1Q6K	-20.53±0.47	-28.97±0.21	-3.85±0.01	28.50±0.33	11.40±0.00
67	1Q9M	-10.80±0.16	-39.34±0.19	-4.74±0.01	30.44±0.28	5.26±0.00
68	1Q41	-17.74±0.30	-39.78±0.23	-4.59±0.01	29.35±0.22	8.78±0.00
69	1QI0	-71.95±0.72	-16.12±0.32	-3.67±0.01	71.86±0.64	14.42±0.00
70	1R6Z	-127.81±0.96	-29.36±0.53	-4.77±0.01	125.32±0.60	22.47±0.01
71	1RIN	-53.09±0.49	-10.79±0.22	-2.67±0.01	53.81±0.40	9.61±0.00
72	1RM8	-65.22±0.47	-40.31±0.33	-5.28±0.01	76.92±0.57	14.31±0.00
73	1RRW	-4.82±0.19	-13.15±0.17	-2.69±0.01	16.00±0.34	4.54±0.01
74	1SQB	-10.36±0.15	-58.89±0.26	-5.95±0.01	38.44±0.28	6.92±0.00
75	1SQN	-25.70±0.35	-49.73±0.23	-4.96±0.01	42.49±0.21	9.16±0.03
76	1SQP	-11.26±0.23	-68.76±0.28	-7.10±0.01	29.68±0.21	8.72±0.00
77	1SQQ	-6.03±0.19	-43.78±0.27	-5.47±0.01	22.28±0.17	6.63±0.00
78	1T7F	-26.46±0.33	-46.20±0.23	-4.74±0.01	39.34±0.17	6.61±0.00
79	1TR7	-94.10±0.51	-17.92±0.35	-3.89±0.01	78.34±0.39	8.37±0.00
80	1TVO	-34.52±0.32	-41.17±0.25	-4.89±0.01	51.49±0.37	-10.81±0.01
81	1U0H	-14.06±0.25	-47.70±0.22	-5.61±0.01	37.83±0.32	7.44±0.00

82	1U3Q	-31.18±0.33	-31.43±0.29	-4.10±0.01	43.48±0.25	7.23±0.00
83	1U3R	-30.18±0.36	-39.54±0.32	-4.53±0.01	42.63±0.18	9.80±0.01
84	1U3S	-32.81±0.25	-37.21±0.28	-4.58±0.01	44.19±0.14	6.50±0.00

Table S3. The binding free energy calculated by two traditional methods and four fitting methods, and their SEMs on the training set. ΔG_{th} is the theoretical values. $\Delta\Delta G=\Delta G_{th}-\Delta G_{exp}$. All values are kcal/mol.

No.	PDBID	Methods												ΔG_{exp}
		ΔG_{PBSA}		$\Delta G_{PBSA+IE}$		ΔG_{H_IE}		$\Delta G_{MM\_Sol\_IE}$		ΔG_{PBSA_IE}		ΔG_{all}		
		ΔG_{th}	$\Delta\Delta G$	ΔG_{th}	$\Delta\Delta G$	ΔG_{th}	$\Delta\Delta G$	ΔG_{th}	$\Delta\Delta G$	ΔG_{th}	$\Delta\Delta G$	ΔG_{th}	$\Delta\Delta G$	
1	1ACJ	-5.29±0.36	5.75	-0.77±0.36	10.27	-6.15±0.05	4.89	-5.98±0.06	5.06	-7.41±0.03	3.63	-7.28±0.03	3.76	-11.04
2	1AYU	-39.91±0.76	-27.41	-25.34±0.76	-12.84	-9.73±0.12	2.77	-9.66±0.12	2.84	-10.34±0.06	2.16	-10.33±0.06	2.17	-12.50
3	1B4D	-32.67±0.92	-26.11	-13.73±0.92	-7.17	-7.91±0.14	-1.35	-7.60±0.14	-1.04	-7.04±0.08	-0.48	-6.86±0.08	-0.30	-6.56
4	1BIO	-9.81±0.69	-2.25	3.25±0.69	10.81	-5.41±0.11	2.15	-5.51±0.11	2.05	-5.79±0.05	1.77	-5.83±0.05	1.73	-7.56
5	1B56	-64.30±0.94	-55.98	-39.69±0.94	-31.37	-11.77±0.14	-3.45	-11.09±0.15	-2.77	-9.06±0.06	-0.74	-8.63±0.07	-0.31	-8.32
6	1BIL	-61.57±0.72	-48.87	-48.03±0.72	-35.33	-13.19±0.11	-0.49	-13.01±0.11	-0.31	-13.58±0.07	-0.88	-13.55±0.07	-0.85	-12.70
7	1C3I	-26.67±1.03	-18.76	-3.22±1.03	4.69	-6.25±0.16	1.66	-4.62±0.16	3.29	-8.31±0.07	-0.40	-6.89±0.07	1.02	-7.91
8	1C85	-32.08±1.27	-25.75	-6.41±1.27	-0.08	-6.70±0.19	-0.37	-6.39±0.20	-0.06	-5.74±0.08	0.59	-5.43±0.09	0.90	-6.33
9	1CR6	-19.00±0.44	-7.38	-9.62±0.44	2.00	-7.42±0.07	4.20	-7.49±0.07	4.13	-8.86±0.04	2.76	-8.89±0.04	2.73	-11.62
10	1CZE	-41.23±2.05	-37.65	-2.38±2.05	1.20	-5.90±0.31	-2.32	-5.57±0.33	-1.99	-3.17±0.12	0.41	-2.97±0.13	0.61	-3.58
11	1D1P	-36.85±1.32	-31.93	-9.33±1.32	-4.41	-7.11±0.20	-2.19	-6.94±0.21	-2.02	-6.09±0.08	-1.17	-5.85±0.09	-0.93	-4.92
12	1DBB	-38.97±0.41	-26.68	-29.50±0.41	-17.21	-10.44±0.06	1.85	-10.64±0.07	1.65	-10.29±0.04	2.00	-10.32±0.04	1.97	-12.29
13	1DBK	-30.64±0.44	-20.95	-22.81±0.44	-13.12	-9.45±0.07	0.24	-9.63±0.07	0.06	-9.25±0.05	0.44	-9.34±0.04	0.35	-9.69
14	1DI9	-30.31±0.46	-23.07	-21.85±0.46	-14.61	-9.29±0.07	-2.05	-9.46±0.07	-2.22	-9.34±0.04	-2.10	-9.50±0.04	-2.26	-7.24
15	1D6N	-8.50±0.44	-2.35	-2.95±0.44	3.20	-6.46±0.07	-0.31	-6.35±0.07	-0.20	-6.56±0.04	-0.41	-6.44±0.04	-0.29	-6.15
16	1E00	-19.72±0.29	-11.40	-15.34±0.29	-7.02	-8.36±0.04	-0.04	-8.47±0.05	-0.15	-8.12±0.03	0.20	-8.27±0.03	0.05	-8.32
17	1E34	-31.62±1.01	-27.69	-5.14±1.01	-1.21	-6.49±0.15	-2.56	-6.38±0.16	-2.45	-6.77±0.06	-2.84	-6.57±0.07	-2.64	-3.93
18	1ENT	-36.58±0.85	-27.08	-17.74±0.85	-8.24	-8.52±0.13	0.98	-8.35±0.14	1.15	-10.45±0.06	-0.95	-10.41±0.07	-0.91	-9.50
19	1ETS	-62.27±1.30	-51.04	-26.98±1.30	-15.75	-9.68±0.20	1.55	-11.00±0.21	0.23	-9.31±0.09	1.92	-10.31±0.09	0.92	-11.23
20	1F0Q	-27.77±0.67	-19.58	-12.32±0.67	-4.13	-7.74±0.10	0.45	-7.95±0.11	0.24	-7.90±0.05	0.29	-7.97±0.05	0.22	-8.19
21	1F2O	-22.57±0.77	-19.97	-9.75±0.77	-7.15	-7.39±0.12	-4.79	-7.42±0.12	-4.82	-6.08±0.06	-3.48	-6.19±0.06	-3.59	-2.60
22	1FBM	-33.10±0.34	-24.60	-26.64±0.34	-18.14	-10.05±0.05	-1.55	-10.22±0.06	-1.72	-10.02±0.03	-1.52	-10.27±0.03	-1.77	-8.50
23	1FJ4	-17.76±0.41	-11.50	-12.37±0.41	-6.11	-7.90±0.06	-1.64	-7.89±0.07	-1.63	-8.53±0.04	-2.27	-8.45±0.04	-2.19	-6.26
24	1FSG	-34.55±0.54	-27.69	-20.83±0.54	-13.97	-9.06±0.08	-2.20	-9.35±0.08	-2.49	-7.26±0.04	-0.40	-7.46±0.04	-0.60	-6.86
25	1FVV	-27.74±0.76	-16.82	-12.80±0.76	-1.88	-7.82±0.12	3.10	-7.81±0.12	3.11	-9.64±0.06	1.28	-9.53±0.06	1.39	-10.92
26	1G27	-38.26±0.74	-27.13	-25.49±0.74	-14.36	-9.78±0.11	1.35	-9.86±0.12	1.27	-8.75±0.06	2.38	-8.89±0.06	2.24	-11.13
27	1G2A	-42.23±1.36	-31.31	-16.69±1.36	-5.77	-8.26±0.21	2.66	-8.70±0.22	2.22	-8.27±0.09	2.65	-8.58±0.10	2.34	-10.92
28	1G4K	-26.14±0.61	-18.36	-14.89±0.61	-7.11	-8.19±0.09	-0.41	-8.35±0.10	-0.57	-8.74±0.05	-0.96	-8.83±0.05	-1.05	-7.78
29	1G50	-36.43±0.56	-27.86	-22.12±0.56	-13.55	-9.25±0.09	-0.68	-9.56±0.09	-0.99	-9.03±0.05	-0.46	-9.20±0.05	-0.63	-8.57
30	1HN2	-22.23±0.28	-14.04	-17.98±0.28	-9.79	-8.76±0.04	-0.57	-8.85±0.04	-0.66	-8.52±0.03	-0.33	-8.56±0.03	-0.37	-8.19
31	1H60	-20.85±0.54	-14.43	-10.61±0.54	-4.19	-7.56±0.08	-1.14	-7.78±0.09	-1.36	-7.70±0.04	-1.28	-7.92±0.04	-1.50	-6.42
32	1H61	-16.83±0.60	-10.16	-5.92±0.60	0.75	-6.84±0.09	-0.17	-6.94±0.10	-0.27	-7.98±0.04	-1.31	-8.11±0.05	-1.44	-6.67
33	1HIV	-67.67±0.93	-55.38	-46.14±0.93	-33.85	-12.79±0.14	-0.50	-12.67±0.15	-0.38	-14.39±0.08	-2.10	-14.25±0.08	-1.96	-12.29
34	1HRN	-41.43±0.96	-30.44	-12.34±0.96	-1.35	-7.55±0.15	3.44	-8.02±0.15	2.97	-9.72±0.07	1.27	-10.04±0.07	0.95	-10.99
35	1I80	-20.51±0.52	-11.76	-13.52±0.52	-4.77	-8.05±0.08	0.70	-7.96±0.08	0.79	-7.03±0.04	1.72	-6.95±0.04	1.80	-8.75
36	1IL3	-23.40±0.43	-19.91	-13.69±0.43	-10.20	-8.03±0.07	-4.54	-8.10±0.07	-4.61	-7.38±0.04	-3.89	-7.33±0.04	-3.84	-3.49

37	1IL4	-23.28±0.47	-19.38	-14.05±0.47	-10.15	-8.10±0.07	-4.20	-8.13±0.07	-4.23	-7.44±0.04	-3.54	-7.36±0.04	-3.46	-3.90
38	1IL9	-26.99±0.57	-22.35	-17.29±0.57	-12.65	-8.58±0.09	-3.94	-8.69±0.09	-4.05	-7.77±0.04	-3.13	-7.76±0.04	-3.12	-4.64
39	1K03	-12.15±0.40	-3.96	-6.21±0.40	1.98	-6.95±0.06	1.24	-6.84±0.06	1.35	-6.64±0.03	1.55	-6.55±0.03	1.64	-8.19
40	1K3T	-19.76±0.48	-14.03	-11.12±0.48	-5.39	-7.66±0.07	-1.93	-7.90±0.08	-2.17	-7.47±0.04	-1.74	-7.74±0.04	-2.01	-5.73
41	1KMV	-23.76±0.75	-14.27	-12.55±0.75	-3.06	-7.84±0.11	1.65	-8.04±0.12	1.45	-9.01±0.05	0.48	-9.17±0.06	0.32	-9.49
42	1LF3	-56.27±0.89	-46.71	-37.16±0.89	-27.60	-11.46±0.13	-1.90	-11.42±0.14	-1.86	-13.12±0.08	-3.56	-13.19±0.08	-3.63	-9.56
43	1LFO	-39.38±1.21	-31.60	-14.36±1.21	-6.58	-7.91±0.18	-0.13	-6.72±0.19	1.06	-7.94±0.08	-0.16	-7.14±0.09	0.64	-7.78
44	1LJT	-28.28±0.59	-21.24	-17.46±0.59	-10.42	-8.59±0.09	-1.55	-8.57±0.09	-1.53	-8.31±0.05	-1.27	-8.25±0.05	-1.21	-7.04
45	1LQD	-27.25±0.78	-16.26	-7.65±0.78	3.34	-6.97±0.12	4.02	-7.81±0.12	3.18	-8.76±0.06	2.23	-9.35±0.06	1.64	-10.99
46	1LT5	-28.47±1.08	-24.78	-4.46±1.08	-0.77	-6.43±0.16	-2.74	-6.76±0.17	-3.07	-6.39±0.07	-2.70	-6.67±0.08	-2.98	-3.69
47	1ME3	-35.91±0.78	-26.09	-18.85±0.78	-9.03	-8.71±0.12	1.11	-8.96±0.12	0.86	-9.47±0.06	0.35	-9.61±0.06	0.21	-9.82
48	1ME4	-40.00±0.81	-30.67	-19.15±0.81	-9.82	-8.70±0.12	0.63	-9.02±0.13	0.31	-8.86±0.06	0.47	-9.11±0.06	0.22	-9.33
49	1MEU	-25.54±0.81	-17.22	-9.95±0.81	-1.63	-7.38±0.12	0.94	-7.43±0.13	0.89	-7.65±0.07	0.67	-7.88±0.07	0.44	-8.32
50	1MS6	-34.14±0.56	-21.14	-23.75±0.56	-10.75	-9.55±0.09	3.45	-9.70±0.09	3.30	-9.64±0.05	3.36	-9.72±0.05	3.28	-13.00
51	1N2V	-33.11±0.69	-27.54	-19.65±0.69	-14.08	-8.89±0.10	-3.32	-8.96±0.11	-3.39	-8.00±0.05	-2.43	-7.99±0.06	-2.42	-5.57
52	1N3W	-42.26±1.04	-32.76	-22.86±1.04	-13.36	-9.29±0.16	0.21	-8.75±0.16	0.75	-7.49±0.09	2.01	-7.21±0.09	2.29	-9.50
53	1NPV	-45.10±0.67	-33.84	-29.84±0.67	-18.58	-10.41±0.10	0.85	-10.00±0.11	1.26	-13.07±0.06	-1.81	-12.55±0.06	-1.29	-11.26
54	1NPZ	-33.35±0.63	-22.58	-22.67±0.63	-11.90	-9.38±0.10	1.39	-9.45±0.10	1.32	-10.29±0.05	0.48	-10.34±0.05	0.43	-10.77
55	1NQC	-29.26±0.63	-19.29	-18.02±0.63	-8.05	-8.67±0.10	1.30	-8.82±0.10	1.15	-9.21±0.06	0.76	-9.38±0.06	0.59	-9.97
56	1O4J	-4.21±0.72	-0.99	6.01±0.72	9.23	-5.04±0.11	-1.82	-5.17±0.12	-1.95	-5.05±0.05	-1.83	-5.25±0.05	-2.03	-3.22
57	1ODY	-41.54±1.05	-30.48	-21.27±1.05	-10.21	-9.03±0.16	2.03	-8.94±0.17	2.12	-11.27±0.08	-0.21	-11.39±0.08	-0.33	-11.06
58	1OFZ	-24.32±1.05	-18.01	-6.43±1.05	-0.12	-6.81±0.16	-0.50	-7.08±0.17	-0.77	-5.40±0.07	0.91	-5.67±0.07	0.64	-6.31
59	1OGU	-37.33±0.62	-27.13	-26.68±0.62	-16.48	-9.99±0.09	0.21	-9.93±0.10	0.27	-10.37±0.05	-0.17	-10.25±0.05	-0.05	-10.20
60	1PCG	-29.73±0.45	-17.85	-22.66±0.45	-10.78	-9.43±0.07	2.45	-9.47±0.07	2.41	-9.28±0.04	2.60	-9.32±0.04	2.56	-11.88
61	1PU8	-14.31±0.53	-10.08	-5.07±0.53	-0.84	-6.73±0.08	-2.50	-6.61±0.08	-2.38	-6.66±0.04	-2.43	-6.54±0.04	-2.31	-4.23
62	1PWY	-22.09±0.70	-16.57	-8.31±0.70	-2.79	-7.16±0.11	-1.64	-7.00±0.11	-1.48	-7.61±0.05	-2.09	-7.39±0.05	-1.87	-5.52
63	1PY5	-35.76±0.48	-25.80	-24.67±0.48	-14.71	-9.68±0.07	0.28	-9.79±0.07	0.17	-9.48±0.04	0.48	-9.46±0.04	0.50	-9.96
64	1Q0B	-29.11±0.36	-22.05	-22.89±0.36	-15.83	-9.48±0.06	-2.42	-9.45±0.06	-2.39	-9.13±0.04	-2.07	-9.09±0.04	-2.03	-7.06
65	1QKU	-35.43±0.45	-22.34	-27.45±0.45	-14.36	-10.15±0.07	2.94	-10.18±0.07	2.91	-9.74±0.04	3.35	-9.71±0.04	3.38	-13.09
66	1Q6K	-24.85±0.61	-14.49	-13.45±0.61	-3.09	-7.97±0.09	2.39	-8.23±0.10	2.13	-7.56±0.04	2.80	-7.77±0.05	2.59	-10.36
67	1Q9M	-24.44±0.38	-15.59	-19.18±0.38	-10.33	-8.93±0.06	-0.08	-8.95±0.06	-0.10	-9.22±0.03	-0.37	-9.24±0.03	-0.39	-8.85
68	1Q41	-32.76±0.44	-22.30	-23.98±0.44	-13.52	-9.61±0.07	0.85	-9.79±0.07	0.67	-9.31±0.04	1.15	-9.43±0.04	1.03	-10.46
69	1QI0	-19.88±1.02	-16.68	-5.46±1.02	-2.26	-6.72±0.15	-3.52	-6.58±0.16	-3.38	-5.74±0.07	-2.54	-5.79±0.07	-2.59	-3.20
70	1R6Z	-36.62±1.25	-29.79	-14.15±1.25	-7.32	-7.92±0.19	-1.09	-7.55±0.20	-0.72	-6.98±0.10	-0.15	-6.78±0.10	0.05	-6.83
71	1RIN	-12.74±0.67	-8.43	-3.13±0.67	1.18	-6.43±0.10	-2.12	-6.29±0.11	-1.98	-5.39±0.05	-1.08	-5.36±0.05	-1.05	-4.31
72	1RM8	-33.89±0.81	-21.60	-19.58±0.81	-7.29	-8.86±0.12	3.43	-8.73±0.13	3.56	-8.80±0.06	3.49	-8.73±0.07	3.56	-12.29
73	1RRW	-4.66±0.43	1.56	-0.12±0.43	6.10	-6.05±0.06	0.17	-6.12±0.07	0.10	-5.76±0.03	0.46	-5.88±0.03	0.34	-6.22
74	1SQB	-36.76±0.41	-25.90	-29.84±0.41	-18.98	-10.53±0.06	0.33	-10.56±0.07	0.30	-11.55±0.04	-0.69	-11.47±0.04	-0.61	-10.86
75	1SQN	-37.90±0.47	-25.07	-28.74±0.47	-15.91	-10.33±0.07	2.50	-10.40±0.07	2.43	-10.49±0.04	2.34	-10.41±0.04	2.42	-12.83
76	1SQP	-57.44±0.42	-46.24	-48.72±0.42	-37.52	-13.36±0.06	-2.16	-13.65±0.07	-2.45	-13.40±0.04	-2.20	-13.58±0.04	-2.38	-11.20
77	1SQQ	-33.00±0.38	-22.32	-26.37±0.38	-15.69	-10.00±0.06	0.68	-10.20±0.06	0.48	-9.95±0.04	0.73	-10.17±0.04	0.51	-10.68
78	1T7F	-38.06±0.44	-27.19	-31.45±0.44	-20.58	-10.77±0.07	0.10	-10.78±0.07	0.09	-10.45±0.04	0.42	-10.36±0.04	0.51	-10.87
79	1TR7	-37.57±0.73	-28.25	-29.20±0.73	-19.88	-10.41±0.11	-1.09	-10.03±0.12	-0.71	-7.55±0.06	1.77	-7.48±0.06	1.84	-9.32

80	1TVO	-29.09±0.55	-19.73	-39.90±0.55	-30.54	-12.31±0.08	-2.95	-11.49±0.09	-2.13	-11.47±0.05	-2.11	-10.91±0.05	-1.55	-9.36
81	1U0H	-29.54±0.46	-20.04	-22.10±0.46	-12.60	-9.34±0.07	0.16	-9.38±0.07	0.12	-10.04±0.04	-0.54	-10.08±0.04	-0.58	-9.50
82	1U3Q	-23.23±0.50	-11.68	-16.00±0.50	-4.45	-8.42±0.08	3.13	-8.35±0.08	3.20	-8.18±0.05	3.37	-8.14±0.05	3.41	-11.55
83	1U3R	-31.62±0.51	-20.29	-21.82±0.51	-10.49	-9.27±0.08	2.06	-9.33±0.08	2.00	-9.11±0.05	2.22	-9.12±0.05	2.21	-11.33
84	1U3S	-30.41±0.40	-18.32	-23.91±0.40	-11.82	-9.63±0.06	2.46	-9.55±0.06	2.54	-9.20±0.04	2.89	-9.15±0.04	2.94	-12.09

Table S4. The energy terms of binding free energy and SEM on the test set. All values are kcal/mol.

NO	PDBID	PBSA				$-T\Delta S_{IE}$
		ΔE_{ele}	ΔE_{vdW}	ΔG_{np}	ΔG_{pb}	
1	1V2H	-42.68±0.45	-20.37±0.22	-3.08±0.01	50.91±0.36	8.38±0.00
2	1V41	-28.30±0.41	-15.79±0.26	-2.96±0.01	34.53±0.29	6.67±0.00
3	1VJY	-23.44±0.32	-47.89±0.24	-4.95±0.01	49.97±0.33	8.17±0.00
4	1VRT	-11.01±0.12	-41.55±0.19	-4.54±0.01	27.71±0.16	5.34±0.01
5	1W7H	-13.75±0.22	-30.00±0.21	-4.11±0.01	24.82±0.28	6.47±0.00
6	1W84	-13.45±0.27	-33.59±0.19	-4.26±0.01	25.13±0.30	6.42±0.00
7	1WBW	-13.14±0.23	-39.13±0.22	-4.52±0.01	27.12±0.20	6.46±0.01
8	1WS5	-68.43±0.61	-17.03±0.29	-3.29±0.01	64.79±0.62	11.53±0.01
9	1WZY	-37.56±0.34	-50.92±0.28	-5.61±0.01	58.97±0.41	10.62±0.00
10	1X7B	-36.96±0.40	-36.75±0.30	-4.47±0.01	50.55±0.22	8.34±0.00
11	1X7E	-17.11±0.26	-38.78±0.18	-4.68±0.01	39.08±0.26	6.15±0.00
12	1XH6	-144.04±0.71	-82.33±0.34	-8.00±0.01	173.92±0.65	20.88±0.00
13	1XLZ	-15.89±0.24	-43.64±0.20	-5.06±0.01	40.49±0.46	5.44±0.00
14	1Y2B	-17.31±0.18	-25.82±0.18	-3.70±0.01	34.66±0.26	4.34±0.00
15	1Y2D	-1.33±0.21	-33.04±0.18	-4.48±0.02	15.72±0.30	4.73±0.00
16	1Y2E	-40.00±0.34	-36.84±0.25	-4.48±0.01	48.37±0.35	9.18±0.00
17	1Z1R	-73.54±0.60	-63.51±0.32	-7.40±0.01	114.20±0.48	15.29±0.01
18	1ZKL	-33.54±0.32	-27.96±0.18	-3.89±0.01	55.21±0.51	9.68±0.00
19	1ZKN	-27.03±0.19	-29.46±0.19	-3.76±0.01	46.87±0.45	5.74±0.00
20	1ZKY	-17.30±0.37	-41.95±0.26	-4.83±0.01	35.53±0.27	8.86±0.00
21	2A2G	-4.38±0.14	-26.62±0.18	-3.67±0.01	17.10±0.14	4.45±0.00
22	2A4G	-44.19±0.52	-59.54±0.34	-7.17±0.01	60.65±0.40	13.65±0.01
23	2AA6	-20.16±0.35	-50.19±0.21	-5.12±0.01	37.07±0.22	7.48±0.00
24	2AI8	-35.20±0.35	-22.66±0.24	-3.54±0.01	46.48±0.39	8.01±0.00
25	2B1Q	-89.00±0.71	-18.81±0.43	-4.29±0.01	95.14±0.63	14.59±0.01
26	2B1V	-20.52±0.40	-32.89±0.23	-4.75±0.01	35.36±0.20	7.18±0.00
27	2BBB	-65.49±0.52	-77.48±0.39	-8.20±0.01	111.70±0.52	12.19±0.00
28	2C5N	-14.85±0.25	-45.19±0.22	-5.24±0.01	32.16±0.21	6.11±0.00
29	2C5O	-9.48±0.19	-31.50±0.17	-3.97±0.01	27.75±0.28	6.31±0.00
30	2CM7	-80.65±0.67	-47.69±0.31	-5.33±0.01	78.88±0.42	16.92±0.01
31	2CNF	-75.14±0.63	-42.39±0.41	-4.72±0.02	71.03±0.42	14.71±0.00
32	2D06	-11.36±0.20	-35.70±0.21	-4.74±0.01	27.96±0.19	5.38±0.01
33	2D2V	-89.14±1.06	-16.82±0.41	-4.10±0.01	99.16±0.83	18.47±0.00
34	2E9N	-21.51±0.56	-47.88±0.30	-5.59±0.01	39.56±0.46	10.28±0.00
35	2ETM	-12.32±0.42	-42.29±0.22	-5.39±0.01	28.68±0.38	9.44±0.00
36	2FAI	-22.11±0.30	-38.96±0.23	-4.74±0.01	35.67±0.19	6.38±0.00
37	2FDD	-49.83±0.45	-72.18±0.35	-8.36±0.02	97.66±0.52	11.31±0.00
38	2G0G	-5.36±0.35	-53.55±0.28	-5.85±0.01	33.87±0.26	5.19±0.00

39	2G1R	-30.99±0.52	-56.00±0.27	-6.12±0.01	52.11±0.41	12.83±0.00
40	2G24	-15.50±0.45	-38.49±0.19	-5.29±0.01	36.31±0.41	10.49±0.00
41	2GH9	-116.01±0.90	-50.79±0.46	-5.91±0.01	122.98±0.57	15.43±0.00
42	2H44	-38.71±0.65	-67.68±0.36	-6.90±0.01	75.81±0.44	13.23±0.00
43	2H96	-16.32±0.31	-46.48±0.24	-5.30±0.01	30.97±0.29	7.24±0.01
44	2HVC	-37.86±0.39	-45.73±0.26	-4.68±0.01	47.23±0.22	8.29±0.01

Table S5. The binding free energy calculated by two traditional methods and four fitting methods, and their SEMs on the training set. ΔG_{th} is the theoretical values. $\Delta\Delta G=\Delta G_{th}-\Delta G_{exp}$. All values are kcal/mol.

No.	PDBID	Methods												ΔG_{th}
		ΔG_{PBSA}		$\Delta G_{PBSA+IE}$		ΔG_{H_IE}		$\Delta G_{MM\_Sol\_IE}$		ΔG_{PBSA_IE}		ΔG_{all}		
		ΔG_{th}	$\Delta\Delta G$	ΔG_{th}	$\Delta\Delta G$	ΔG_{th}	$\Delta\Delta G$	ΔG_{th}	$\Delta\Delta G$	ΔG_{th}	$\Delta\Delta G$	ΔG_{th}	$\Delta\Delta G$	
1	1V2H	-15.22±0.62	-7.98	-6.84±0.62	0.40	-7.01±0.09	0.23	-6.87±0.10	0.37	-6.57±0.05	0.67	-6.46±0.05	0.78	-7.24
2	1V41	-12.52±0.57	-6.10	-5.85±0.57	0.57	-6.89±0.09	-0.47	-6.85±0.09	-0.43	-6.19±0.05	0.23	-6.23±0.05	0.19	-6.42
3	1VJY	-26.31±0.52	-15.88	-18.14±0.52	-7.71	-8.73±0.08	1.70	-8.64±0.08	1.79	-9.80±0.04	0.63	-9.60±0.04	0.83	-10.43
4	1VRT	-29.39±0.27	-19.70	-24.05±0.27	-14.36	-9.67±0.04	0.02	-9.73±0.04	-0.04	-9.69±0.03	0.00	-9.68±0.03	0.01	-9.69
5	1W7H	-23.04±0.41	-18.94	-16.57±0.41	-12.47	-8.52±0.06	-4.42	-8.63±0.07	-4.53	-8.12±0.04	-4.02	-8.26±0.04	-4.16	-4.10
6	1W84	-26.17±0.45	-20.09	-19.75±0.45	-13.67	-9.00±0.07	-2.92	-9.12±0.07	-3.04	-8.64±0.04	-2.56	-8.75±0.04	-2.67	-6.08
7	1WBW	-29.67±0.37	-23.72	-23.21±0.37	-17.26	-9.53±0.06	-3.58	-9.64±0.06	-3.69	-9.35±0.04	-3.40	-9.41±0.04	-3.46	-5.95
8	1WS5	-23.96±0.92	-19.82	-12.43±0.92	-8.29	-7.82±0.14	-3.68	-7.66±0.15	-3.52	-6.37±0.06	-2.23	-6.35±0.07	-2.21	-4.14
9	1WZY	-35.12±0.60	-26.58	-24.50±0.60	-15.96	-9.66±0.09	-1.12	-9.60±0.10	-1.06	-10.29±0.05	-1.75	-10.18±0.05	-1.64	-8.54
10	1X7B	-27.63±0.55	-16.18	-19.29±0.55	-7.84	-8.90±0.08	2.55	-8.81±0.09	2.64	-8.80±0.05	2.65	-8.71±0.05	2.74	-11.45
11	1X7E	-21.49±0.41	-13.33	-15.34±0.41	-7.18	-8.34±0.06	-0.18	-8.28±0.06	-0.12	-8.91±0.03	-0.75	-8.85±0.03	-0.69	-8.16
12	1XH6	-60.45±1.02	-50.46	-39.57±1.02	-29.58	-11.80±0.15	-1.81	-10.93±0.16	-0.94	-13.46±0.07	-3.47	-12.54±0.08	-2.55	-9.99
13	1XLZ	-24.10±0.56	-15.88	-18.66±0.56	-10.44	-8.85±0.08	-0.63	-8.76±0.09	-0.54	-9.59±0.04	-1.37	-9.50±0.04	-1.28	-8.22
14	1Y2B	-12.17±0.37	-6.59	-7.83±0.37	-2.25	-7.22±0.06	-1.64	-7.10±0.06	-1.52	-7.38±0.03	-1.80	-7.32±0.03	-1.74	-5.58
15	1Y2D	-23.13±0.40	-15.35	-18.40±0.40	-10.62	-8.82±0.06	-1.04	-8.98±0.07	-1.20	-8.61±0.03	-0.83	-8.81±0.03	-1.03	-7.78
16	1Y2E	-32.95±0.55	-23.67	-23.77±0.55	-14.49	-9.57±0.08	-0.29	-9.56±0.09	-0.28	-9.00±0.05	0.28	-8.98±0.05	0.30	-9.28
17	1Z1R	-30.25±0.83	-17.66	-14.96±0.83	-2.37	-8.15±0.13	4.44	-7.64±0.13	4.95	-10.69±0.06	1.90	-10.27±0.06	2.32	-12.59
18	1ZKL	-10.18±0.63	-3.23	-0.50±0.63	6.45	-6.03±0.10	0.92	-5.88±0.10	1.07	-6.87±0.04	0.08	-6.74±0.05	0.21	-6.95
19	1ZKN	-13.38±0.52	-7.22	-7.64±0.52	-1.48	-7.17±0.08	-1.01	-6.97±0.08	-0.81	-7.63±0.04	-1.47	-7.45±0.04	-1.29	-6.16
20	1ZKY	-28.55±0.52	-20.01	-19.69±0.52	-11.15	-8.96±0.08	-0.42	-9.06±0.08	-0.52	-9.28±0.05	-0.74	-9.33±0.04	-0.79	-8.54
21	2A2G	-17.57±0.27	-8.01	-13.12±0.27	-3.56	-8.02±0.04	1.54	-8.13±0.04	1.43	-7.74±0.03	1.82	-7.85±0.03	1.71	-9.56
22	2A4G	-50.25±0.74	-40.45	-36.60±0.74	-26.80	-11.45±0.11	-1.65	-11.55±0.12	-1.75	-11.58±0.06	-1.78	-11.74±0.06	-1.94	-9.80
23	2AA6	-38.40±0.47	-25.55	-30.92±0.47	-18.07	-10.68±0.07	2.17	-10.75±0.07	2.10	-10.75±0.04	2.10	-10.70±0.04	2.15	-12.85
24	2AI8	-14.92±0.57	-5.64	-6.91±0.57	2.37	-7.03±0.09	2.25	-6.92±0.09	2.36	-6.82±0.05	2.46	-6.78±0.05	2.50	-9.28
25	2B1Q	-16.96±1.04	-14.80	-2.37±1.04	-0.21	-6.24±0.16	-4.08	-5.85±0.17	-3.69	-5.82±0.08	-3.66	-5.71±0.08	-3.55	-2.16
26	2B1V	-22.80±0.50	-14.96	-15.62±0.50	-7.78	-8.36±0.08	-0.52	-8.39±0.08	-0.55	-8.31±0.04	-0.47	-8.43±0.04	-0.59	-7.84
27	2BBB	-39.47±0.83	-27.70	-27.28±0.83	-15.51	-10.06±0.13	1.71	-9.50±0.13	2.27	-12.86±0.07	-1.09	-12.33±0.07	-0.56	-11.77
28	2C5N	-33.12±0.39	-24.03	-27.01±0.39	-17.92	-10.11±0.06	-1.02	-10.17±0.06	-1.08	-10.15±0.04	-1.06	-10.20±0.04	-1.11	-9.09
29	2C5O	-17.20±0.38	-10.12	-10.89±0.38	-3.81	-7.66±0.06	-0.58	-7.71±0.06	-0.63	-7.97±0.03	-0.89	-8.00±0.03	-0.92	-7.08
30	2CM7	-54.79±0.85	-45.67	-37.87±0.85	-28.75	-11.60±0.13	-2.48	-11.61±0.13	-2.49	-10.33±0.06	-1.21	-10.28±0.06	-1.16	-9.12
31	2CNF	-51.22±0.85	-42.18	-36.51±0.85	-27.47	-11.43±0.13	-2.39	-11.42±0.13	-2.38	-9.88±0.07	-0.84	-9.82±0.07	-0.78	-9.04
32	2D06	-23.84±0.34	-18.27	-18.46±0.34	-12.89	-8.82±0.05	-3.25	-8.87±0.05	-3.30	-8.83±0.03	-3.26	-8.94±0.03	-3.37	-5.57
33	2D2V	-10.90±1.40	-9.53	7.57±1.40	8.94	-4.68±0.21	-3.31	-4.37±0.22	-3.00	-4.86±0.09	-3.49	-4.79±0.10	-3.42	-1.37
34	2E9N	-35.42±0.79	-24.21	-25.14±0.79	-13.93	-9.76±0.12	1.45	-9.91±0.13	1.30	-10.05±0.06	1.16	-10.17±0.06	1.04	-11.21
35	2ETM	-31.32±0.61	-22.21	-21.88±0.61	-12.77	-9.28±0.09	-0.17	-9.50±0.10	-0.39	-9.40±0.04	-0.29	-9.64±0.05	-0.53	-9.11
36	2FAI	-30.14±0.42	-21.61	-23.76±0.42	-15.23	-9.61±0.06	-1.08	-9.63±0.07	-1.10	-9.37±0.04	-0.84	-9.39±0.04	-0.86	-8.53

37	2FDD	-32.71±0.77	-21.35	-21.40±0.77	-10.04	-9.18±0.12	2.18	-8.73±0.12	2.63	-12.09±0.06	-0.73	-11.77±0.06	-0.41	-11.36
38	2G0G	-30.89±0.51	-22.30	-25.70±0.51	-17.11	-9.92±0.08	-1.33	-9.93±0.08	-1.34	-10.92±0.05	-2.33	-10.89±0.05	-2.30	-8.59
39	2G1R	-41.00±0.71	-30.49	-28.17±0.71	-17.66	-10.19±0.11	0.32	-10.31±0.11	0.20	-10.83±0.05	-0.32	-10.87±0.06	-0.36	-10.51
40	2G24	-22.97±0.64	-15.60	-12.48±0.64	-5.11	-7.84±0.10	-0.47	-7.99±0.10	-0.62	-8.47±0.04	-1.10	-8.67±0.05	-1.30	-7.37
41	2GH9	-49.73±1.16	-41.54	-34.30±1.16	-26.11	-11.08±0.18	-2.89	-10.52±0.18	-2.33	-10.52±0.09	-2.33	-10.06±0.09	-1.87	-8.19
42	2H44	-37.48±0.86	-29.60	-24.25±0.86	-16.37	-9.59±0.13	-1.71	-9.45±0.14	-1.57	-11.70±0.07	-3.82	-11.46±0.07	-3.58	-7.88
43	2H96	-37.13±0.48	-28.07	-29.89±0.48	-20.83	-10.53±0.07	-1.47	-10.66±0.08	-1.60	-10.36±0.04	-1.30	-10.45±0.04	-1.39	-9.06
44	2HVC	-41.04±0.52	-28.99	-32.75±0.52	-20.70	-10.95±0.08	1.10	-10.94±0.08	1.11	-10.38±0.05	1.67	-10.26±0.04	1.79	-12.05

Table S6. Individual energy terms and total binding free energy for 10 protein–ligand complexes in the 2 ns and 10 ns MD simulations. MAE[a] is the MAE of various energy term between 2 ns and 10 ns MD simulation for each system. MAE[b] is the MAE of all systems between 2 ns and 10 ns MD simulation for each energy term.

PDBID	2 ns					10 ns					MAE[a]
	ΔG_{ele+pb}	ΔE_{vdW}	ΔG_{np}	$-T\Delta S_{IE}$	ΔG_{th}	ΔG_{ele+pb}	ΔE_{vdW}	ΔG_{np}	$-T\Delta S_{IE}$	ΔG_{th}	
1DBB	13.21±0.34	-47.4±0.24	-4.78±0.01	9.47±0.00	-29.50±0.41	14.72±0.43	-47.61±0.22	-4.70±0.01	9.09±0.00	-28.50±0.48	0.64
1E00	13.71±0.23	-29.39±0.17	-4.04±0.01	4.38±0.00	-15.34±0.29	14.71±0.16	-29.65±0.17	-4.03±0.01	4.49±0.00	-14.48±0.23	0.45
1FBM	16.90±0.27	-44.27±0.21	-5.73±0.01	6.46±0.00	-26.64±0.34	14.56±0.22	-44.19±0.21	-5.68±0.01	6.21±0.00	-29.10±0.31	1.03
1FVV	31.63±0.71	-53.5±0.27	-5.87±0.02	14.94±0.01	-12.80±0.76	28.38±0.92	-52.31±0.35	-5.74±0.01	16.06±0.00	-13.61±0.99	1.30
1IL9	4.02±0.52	-27.84±0.23	-3.17±0.00	9.70±0.00	-17.29±0.57	4.48±0.36	-26.61±0.25	-3.17±0.00	7.83±0.00	-17.47±0.44	0.75
1OFZ	-7.21±1.01	-14.2±0.28	-2.91±0.01	17.89±0.01	-6.43±1.05	-7.04±0.87	-13.90±0.28	-2.91±0.00	18.05±0.01	-5.80±0.91	0.25
1PY5	11.34±0.40	-42.57±0.26	-4.53±0.01	11.09±0.00	-24.67±0.48	10.30±0.39	-41.00±0.26	-4.55±0.01	11.18±0.01	-24.07±0.47	0.67
1DI9	15.85±0.39	-41.1±0.25	-5.06±0.01	8.46±0.01	-21.85±0.46	14.08±0.53	-37.15±0.25	-5.00±0.01	8.88±0.00	-19.19±0.58	1.77
1Q41	11.61±0.37	-39.78±0.23	-4.59±0.01	8.78±0.00	-23.98±0.44	9.61±0.34	-36.56±0.23	-4.53±0.01	7.61±0.00	-22.32±0.41	1.62
1PCG	14.16±0.37	-39.16±0.26	-4.73±0.01	7.07±0.00	-22.66±0.45	13.95±0.44	-40.99±0.25	-4.72±0.01	9.16±0.00	-22.6±0.51	0.84
MAE[b]	1.38	1.38	0.04	0.77	1.09						

$\Delta G_{ele+pb}=\Delta E_{ele}+\Delta G_{pb}$

Figure Captions

Figure S1. the RMSD of the protein backbone as a function of simulation time and the native structure of the three representative systems in the training set.

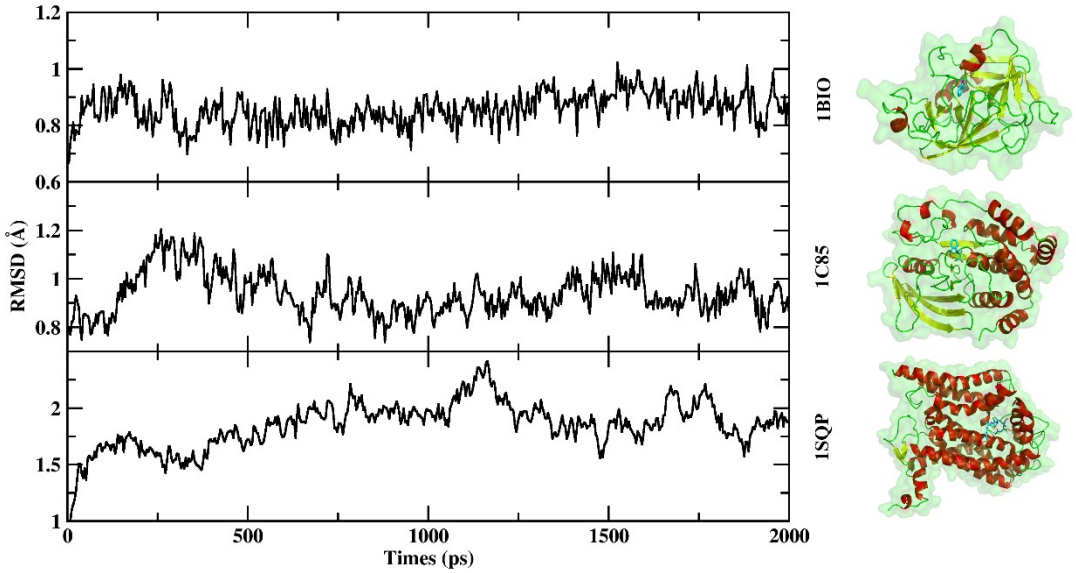


Figure S2. The RMSD of the protein backbone as a function of simulation time and the native structure of the three representative systems in the test set.

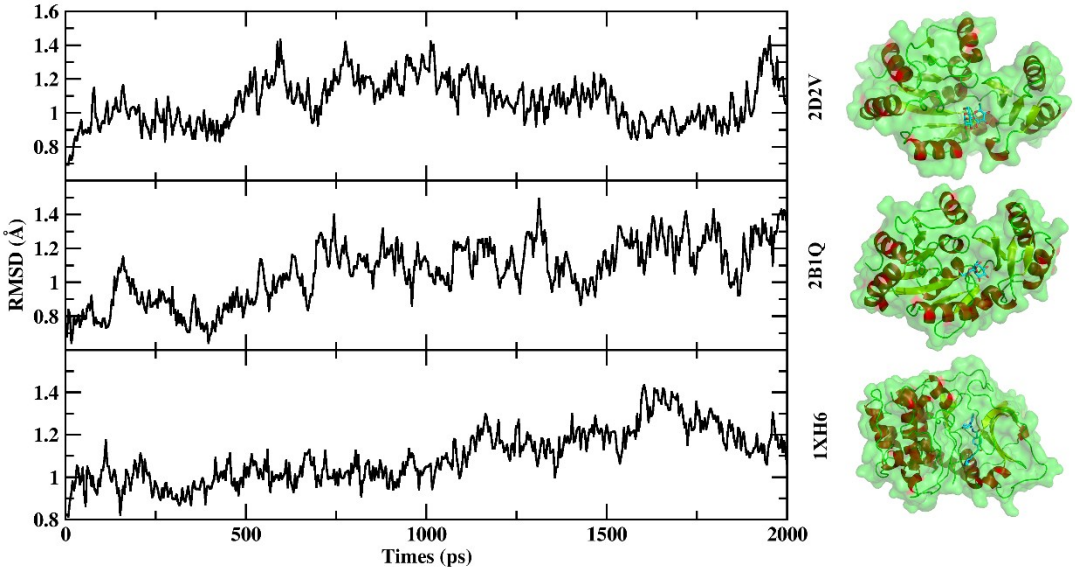
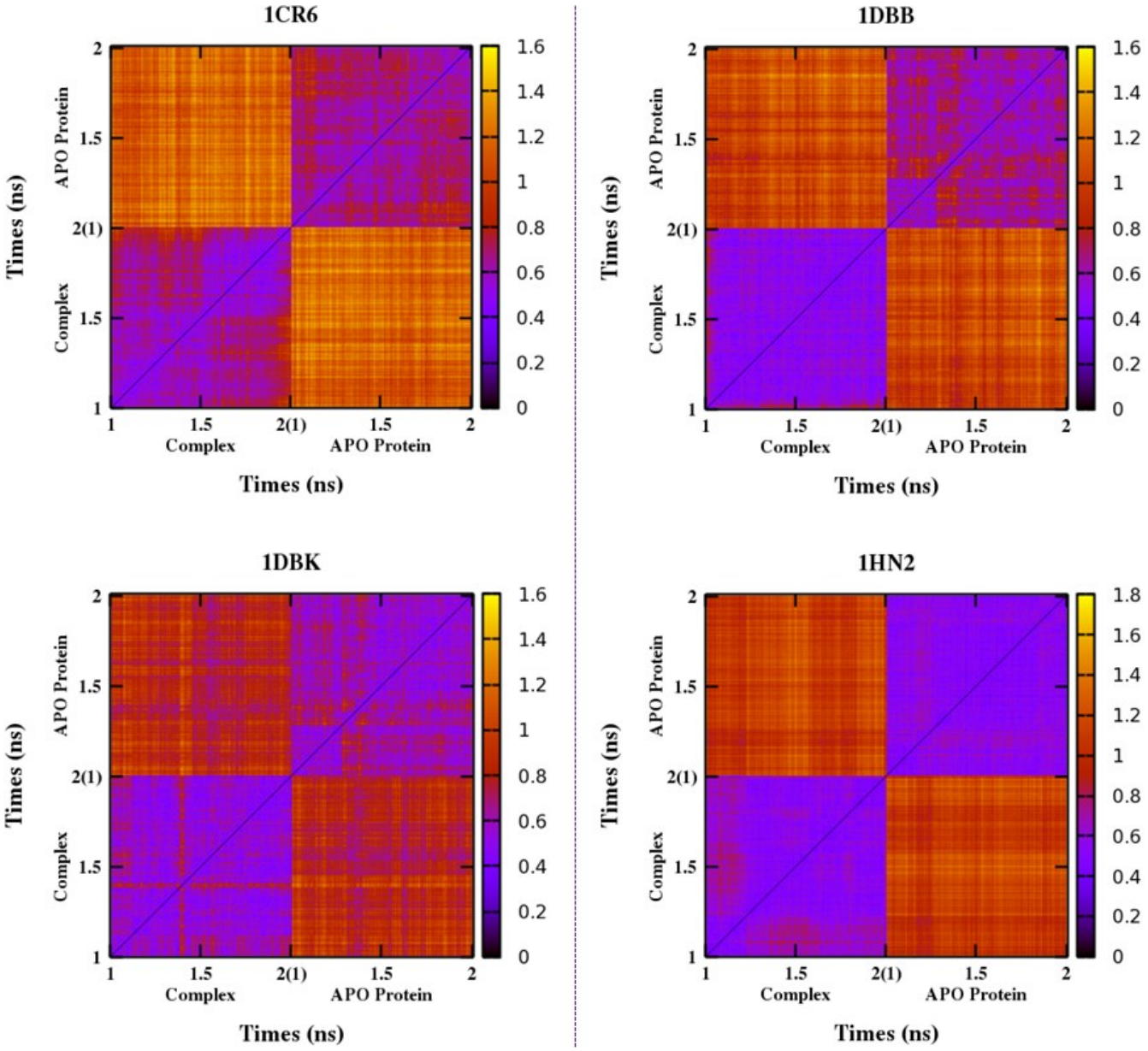
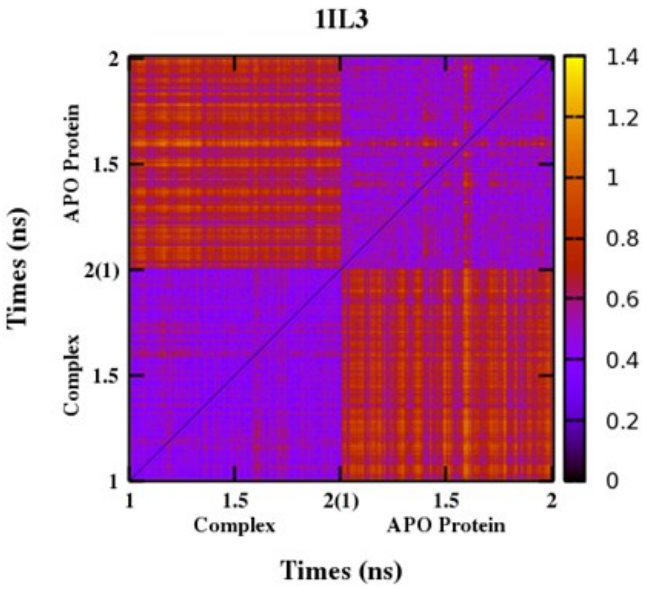


Figure S3. Cross-comparison of 2D-RMSD of binding pocket for Cα atoms between the protein-ligand complex and apo protein in training set. All values are Å.

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2(1)
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1.4
1.2
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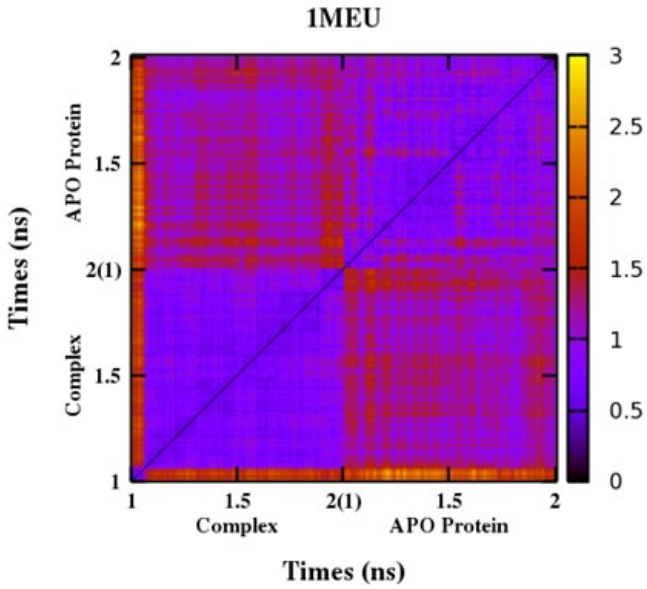
0.8
0.6
0.4
0.2
0
Complex
APO Protein
Times (ns)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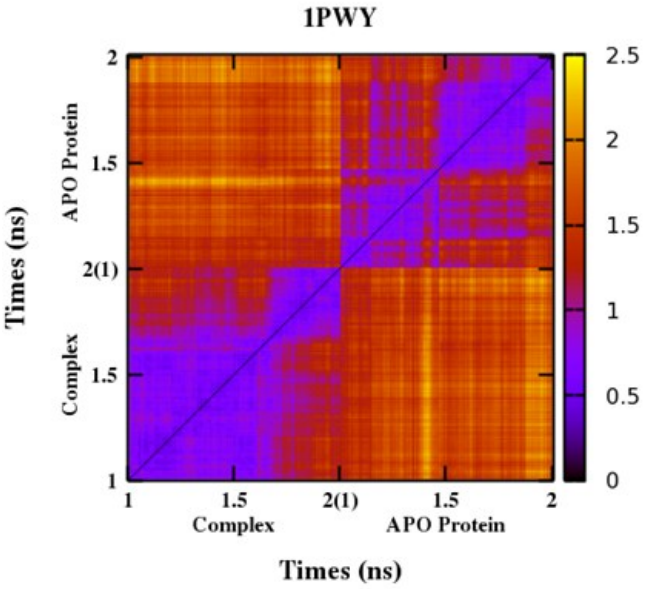
Times (ns)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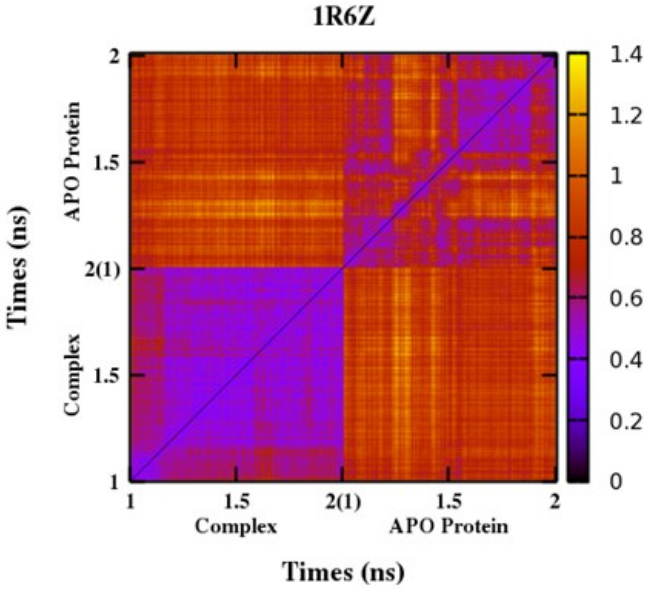
Times (ns)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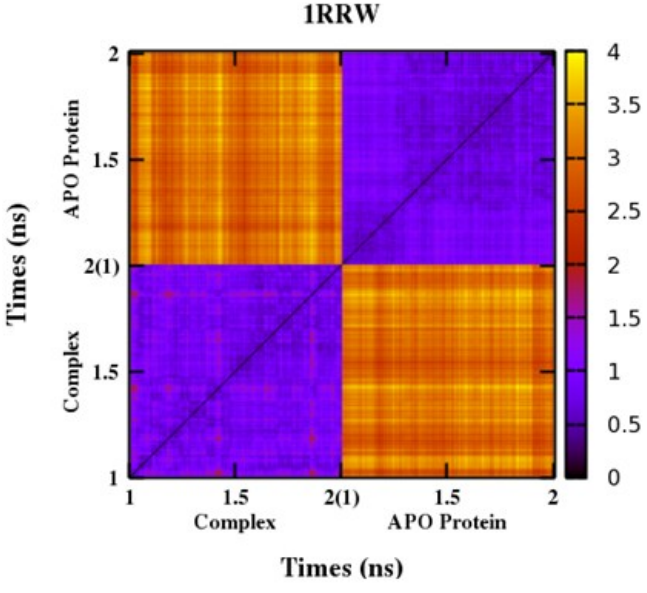
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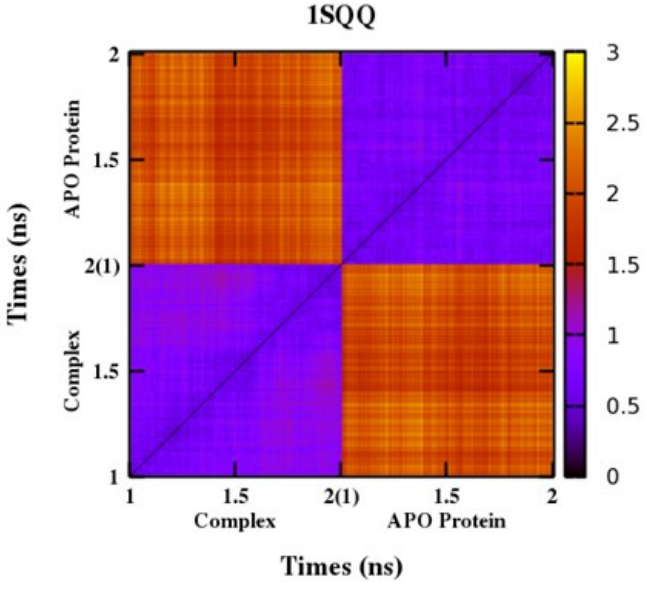
APO Protein
Times (ns)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APO Protein
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2(1)
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2
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2.5
2
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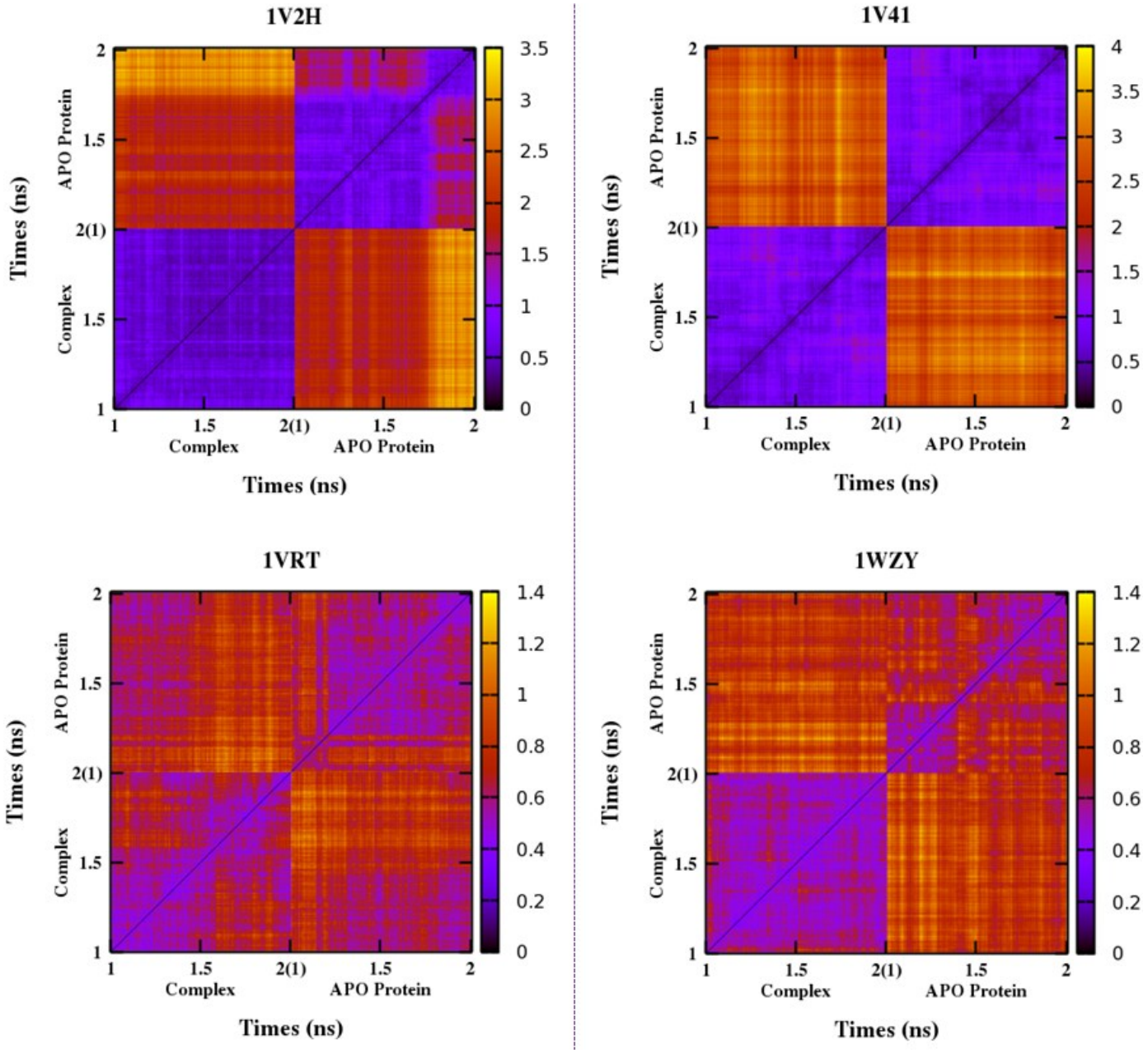
1
0.5
0
Complex
APO Protein
Times (ns)

Figure S4. Cross-comparison of 2D-RMSD of binding pocket for Cα atoms between the protein-ligand complex and apo protein in test set. All values are Å.



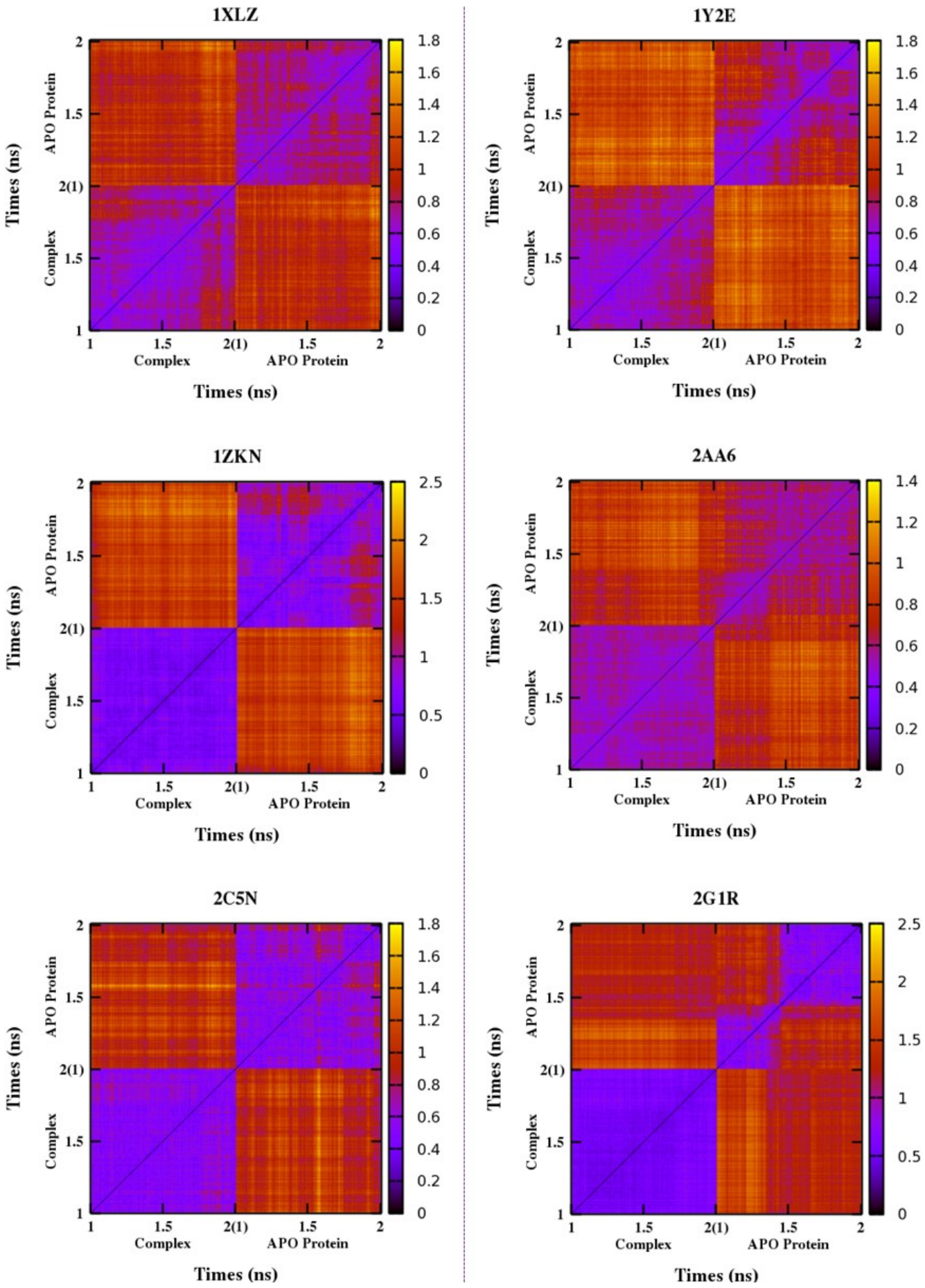

1XLZ
1Y2E
1ZKN
2AA6
2C5N
2G1R
Times (ns)
APO Protein
Complex
1
1.5
2(1)
2

Figure S5. RMSFs of binding pocket for Cα atoms for the 10 protein-ligand complex and apo protein in the training set.

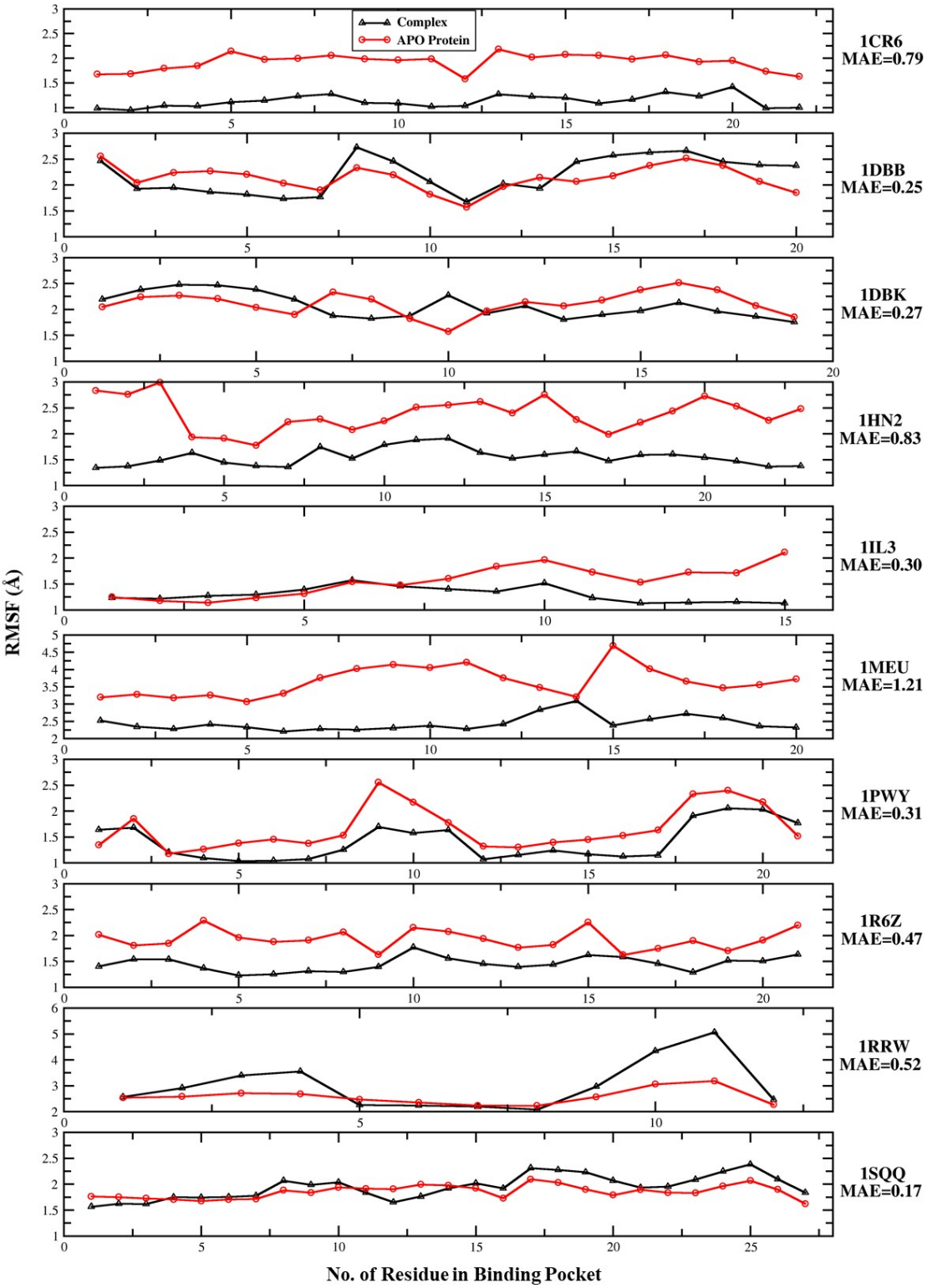


Figure S6. RMSFs of binding pocket for Cα atoms for the 10 protein-ligand complex and apo protein in the test set.