Supporting Information:

PANTHER - **P**rotein-**A**ffinity for **N**ucleic **T**arget-binding, **H**ybridization, and **E**nergy **R**egression

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Table S1. Train Set and Experimental ΔG, Data not Available (DNoA)

Train Set	MD-derived local-to-global score (kcal/mol)	Experimental ΔG (kcal/mol)
1ASZ	-4.88	-10.25
1EXD	-7.30	-13.04
1KNZ	-6.86	-9.61
1JBT	-	DNoA
1KUQ	-	DNoA
1N77	-5.39	-5.52
1OOA	-7.02	-11.27
1SJ4	-	DNoA
1ZL3	-	DNoA
2AB4	-	DNoA
2ASB	-	DNoA
2ATW	-	DNoA
2JLW	-	DNoA
2LEB	-5.65	-9.31
2UMW	-	DNoA
2XFM	-5.91	-8.24
2XLK	-	DNoA
2Y8W	-7.78	-11.39
2F8K	-6.25	-10.37
2ZUE	-	DNoA
3K49	-5.70	-8.74
3T5N	-	DNoA

3UMY	-	DNoA
4AL5	-8.91	-14.04
4M6D	-	DNoA
4ZLD	-	DNoA
5GJB	-	DNoA
5HO4	-	DNoA
5MFX	-	DNoA
5WT1	-	DNoA
6DU4	-	DNoA
6F4H	-	DNoA
6FQ3	3.28	-8.02
6IV9	-	DNoA
6KYV	-	DNoA
6LAX	-	DNoA
6SDW	-6.48	-10.92
6ZDQ	-	DNoA
7A9W	-	DNoA
7EIU	-	DNoA
7OZQ	-	DNoA
7P0V	-	DNoA
7v2Z	-	DNoA
7VKL	-	DNoA
7XJZ	-	DNoA
7ZEX	-	DNoA

Table S2 Pearson correlation coefficient (r) between raw MD-derived predicted local energies vs raw ML-derived predicted local energies for various models for each PDB IDs considered in the test set, refer to Figure S3 for an example of 1EC6. This correlation study was done to see how well the ML models predict the MD-derived local energies. The data from the test set used to predict the local energies through ML models are derived from the MD simulations.

Test Set	**(r) Random Forest prediction vs MD-derived local energies**	**(r) GBoost prediction vs MD-derived local energies**	**(r) Neural Network prediction vs MD-derived local energies**	**(r) Stacked Ensemble prediction vs MD-derived local energies**	**(r) XGBoost prediction vs MD-derived local energies**	**(r) Linear Regression prediction vs MD-derived local energies**	**Mean (r)**
1U0B	0.74	0.76	0.78	0.75	0.77	0.72	0.75
1RKJ	0.65	0.67	0.68	0.67	0.68	0.67	0.67
1NYB	0.78	0.79	0.83	0.79	0.80	0.76	0.79
1EC6	0.80	0.82	0.84	0.82	0.84	0.76	0.81
2B6G	0.63	0.64	0.74	0.65	0.67	0.77	0.68
2LBS	0.46	0.50	0.68	0.57	0.60	0.60	0.57
2M8D	0.74	0.73	0.81	0.74	0.79	0.77	0.76
Mean	0.69	0.70	0.77	0.71	0.74	0.72	0.72

Table S3 Test set, Experimental ΔG (kcal/mol) and predicted model-specific PANTHER score (kcal/mol) from various models. The data from the test set used to predict the local energies through ML models are derived from the MD simulations.

Test Set	Exp. ΔG (kcal/mol)	MD-derived local-to-global Score (kcal/mol)	Model-specific Random Forest PANTHER score (kcal/mol)	Model-specific GBoost PANTHER score (kcal/mol)	Model-specific Neural Network PANTHER score (kcal/mol)	Model-specific Stacked Ensemble PANTHER score (kcal/mol)	Model-specific XGBoost PANTHER score (kcal/mol)	Model-specific Linear Regression PANTHER score (kcal/mol)	PredPRBA (kcal/mol)	PRA-Pred (kcal/mol)
1U0B	-8.96	-6.38	-6.25	-6.35	-6.32	-6.35	-6.36	-6.23	-13.92	-11.07
1RKJ	-7.99	-7.46	-7.07	-7.15	-7.33	-7.23	-7.28	-7.43	-11.17	-10.48
1NYB	-9.13	-8.47	-7.67	-7.87	-8.05	-7.84	-7.99	-7.62	-10.31	-9.58
1EC6	-7.99	-5.19	-6.00	-6.11	-6.06	-6.08	-6.03	-6.25	-8.68	-8.48
2B6G	-10.26	-7.06	-7.53	-7.62	-7.38	-7.56	-7.49	-7.39	-10.85	-8.37
2LBS	-6.09	-5.33	-5.39	-5.42	-5.70	-5.52	-5.65	-5.69	-12.10	-8.98
2M8D	-8.73	-6.82	-6.72	-6.65	-7.17	-6.82	-6.94	-7.18	-9.14	-7.17
(r)		0.59	0.80	0.79	0.68	0.77	0.72	0.69	-0.10	-0.06

Table S4. Stress Data Set, Experimental ΔG (kcal/mol) and Predicted model-specific PANTHER score (kcal/mol) *from various models, and Data not Available (DNoA)*

Stress Data Set	Exp. ΔG	Random Forest	GBoost	Neural Network	Stacked Ensemble	XGBoost	Linear Regression	PredPRBA	PRA-Pred
1C9S	-12.91	-10.10	-9.44	-24.10	-12.34	-11.03	-52.35	-14.83	DNoA
1CVJ	-10.92	-10.34	-9.88	-19.39	-12.93	-11.77	-34.63	-8.21	-8.74
1IL2	-7.53	-6.13	-5.80	-6.74	-6.06	-6.14	-7.03	DNoA	-8.77
1JBS	-8.18	-8.44	-7.86	-9.42	-8.48	-8.48	-10.67	-11.63	-8.34
1K1G	-8.18	-7.05	-6.82	-8.72	-7.58	-7.23	-9.69	-10.27	-9.33
1K8W	-8.73	-6.06	-5.88	-6.36	-5.98	-6.01	-6.84	-8.75	-9.66
1KQ2	-9.89	-8.58	-8.49	-13.55	-9.98	-9.86	-17.93	-9.86	-10.71
1MMS	-9.44	-6.70	-6.38	-8.37	-7.00	-6.96	-9.69	-13.45	-10.27
1QTQ	-9.13	-6.66	-6.51	-6.94	-6.59	-6.67	-7.03	-14.30	-11.44
1RLG	-7.99	-7.35	-6.90	-10.14	-7.85	-7.67	-12.82	-10.42	-9.22
1SDS	-9.03	-7.68	-6.55	-11.48	-8.38	-8.07	-14.19	-11.78	-9.23
1UTD	-11.81	-9.60	-9.34	-17.42	-11.37	-10.51	-32.24	DNoA	DNoA
1WSU	-12.97	-10.84	-9.99	-13.57	-11.40	-10.68	-16.45	-7.94	-10.87
1WWD	-8.18	-7.87	-6.54	-9.34	-7.60	-7.32	-10.49	-7.81	-6.36
1YTU	-6.87	-8.06	-7.38	-9.41	-8.23	-8.50	-9.81	-7.96	-12.37
1YTY	-9.16	-6.61	-6.27	-8.39	-6.85	-6.79	-9.46	-8.96	-8.68
2A8V	-7.22	-7.30	-6.83	-10.73	-6.69	-6.69	-11.87	-9.08	-8.09
2C4R	-9.50	-6.67	-6.29	-8.19	-6.52	-6.67	-8.40	-10.68	-10.55
2DRB	-9.78	-5.64	-5.48	-5.80	-5.35	-5.56	-6.13	-12.30	-9.73
2I91	-8.86	-7.91	-7.29	-8.90	-7.92	-7.91	-10.60	-11.06	-12.31
2IX1	-10.48	-6.27	-5.87	-6.87	-6.34	-6.26	-7.14	-8.41	-9.95
2JEA	-7.98	-6.52	-6.23	-8.95	-6.81	-6.90	-8.99	-9.81	-10.75
2KX5	-11.41	-9.78	-9.54	-11.21	-9.90	-10.14	-11.22	-11.66	-7.74
2L41	-4.25	-6.79	-5.97	-8.89	-7.19	-6.87	-9.85	-8.82	-8.89

2LA5	-11.48	-10.19	-9.15	-11.05	-10.03	-10.18	-11.31	-13.45	-7.65
2LEC	-9.44	-8.19	-7.36	-10.38	-8.23	-7.93	-10.81	-7.96	-6.80
2MB0	-6.80	-6.91	-6.46	-7.67	-7.07	-7.04	-7.99	-7.81	-6.83
2PJP	-12.98	-8.63	-8.64	-8.81	-8.54	-8.38	-8.34	-12.35	-10.59
2UWM	-7.09	-7.91	-7.86	-9.34	-8.32	-8.40	-10.33	-12.16	-10.43
2X1A	-7.13	-6.75	-7.51	-8.72	-7.06	-7.38	-9.04	-5.87	-7.24
2XC7	-7.07	-7.06	-7.55	-8.09	-7.56	-7.76	-8.37	-8.05	-8.55
2XGJ	-7.70	-9.00	-9.08	-10.16	-9.91	-9.81	-10.98	-10.09	-13.25
2XNR	-5.40	-5.27	-5.05	-6.40	-5.50	-5.43	-6.81	-9.25	-7.42
2XS2	-10.11	-7.42	-7.11	-9.61	-7.57	-7.40	-10.60	-8.92	-8.18
2ZZN	-9.24	-7.34	-6.94	-8.17	-7.29	-7.20	-9.04	DNoA	-9.48
3ADB	-9.81	-6.14	-5.77	-6.88	-5.86	-6.09	-7.49	-14.00	-17.12
3BX2	-9.97	-7.23	-5.95	-10.27	-7.32	-6.85	-12.74	-9.96	-9.37
3D2S	-9.38	-8.82	-8.73	-12.09	-9.07	-9.18	-15.66	-9.02	DNoA
3IEV	-10.76	-7.47	-7.03	-7.41	-6.96	-7.14	-7.56	-9.63	-9.01
3K61	-8.89	-6.44	-5.97	-7.14	-6.37	-6.36	-7.22	-8.94	-10.37
3K62	-8.74	-6.67	-6.15	-7.45	-6.75	-6.55	-7.74	-8.79	-9.85
3L25	-8.59	-7.35	-6.53	-8.74	-6.95	-7.11	-10.06	-9.65	-11.54
3MDG	-7.27	-5.45	-5.73	-5.75	-5.41	-5.56	-6.13	-7.33	-8.71
3NMR	-8.44	-6.63	-6.68	-7.23	-6.50	-6.77	-7.31	-8.44	-7.66
3O3I	-6.52	-3.98	-3.92	-4.56	-3.93	-3.99	-5.61	-10.03	-7.87
3O8C	-8.26	-5.09	-4.84	-5.48	-4.93	-4.93	-5.86	-10.09	-12.48
3PF5	-8.53	-5.27	-5.58	-6.76	-5.44	-5.73	-7.76	-7.83	-6.97
3Q0P	-12.81	-8.44	-7.46	-11.76	-8.54	-8.54	-14.77	-8.90	-10.21
3QG9	-10.56	-6.16	-5.63	-6.87	-6.21	-6.17	-7.13	-9.28	-9.91
3R2C	-10.63	-9.30	-8.97	-12.38	-9.46	-9.43	-15.65	-9.50	-10.05
3SIU	-9.17	-7.94	-7.46	-9.71	-8.18	-8.13	-11.61	-14.01	-10.02
3TRZ	-11.04	-10.46	-9.59	-17.44	-11.63	-10.92	-28.53	-10.55	-9.36
4ALP	-10.02	-10.51	-9.39	-12.15	-8.42	-9.55	-15.32	-8.08	DNoA
4B8T	-7.13	-6.26	-5.57	-7.46	-5.73	-5.89	-7.52	-9.21	-8.62
4C7O	-8.59	-5.76	-5.57	-6.04	-5.46	-5.67	-6.35	DNoA	-12.43
4CQN	-5.76	-6.03	-5.73	-7.01	-5.91	-6.10	-7.99	-13.68	-15.29
4CSF	-8.98	-9.54	-8.01	-24.35	-11.43	-10.08	-51.52	-9.88	-16.34
4ED5	-9.08	-7.72	-6.52	-9.87	-7.80	-7.52	-12.27	-9.63	-8.41
4ERD	-9.54	-8.31	-8.52	-10.40	-9.00	-9.02	-11.37	-9.47	-9.46
4G0A	-10.18	-9.37	-9.17	-12.67	-10.38	-10.11	-14.07	-9.94	-12.69
4GHA	-6.92	-5.32	-5.29	-6.37	-5.60	-5.43	-7.19	-10.38	-10.80
4GHL	-7.06	-4.78	-4.52	-5.25	-4.38	-4.31	-5.87	-11.89	DNoA
4H5P	-9.56	-8.86	-6.61	-14.32	-9.42	-8.65	-19.54	-9.55	-11.57
4I67	-6.76	-5.06	-5.27	-5.54	-4.95	-5.42	-5.65	-8.63	-7.93
4J1G	-9.09	-8.15	-7.07	-12.47	-8.81	-8.19	-17.11	-11.80	-18.30
4JVY	-9.76	-9.14	-8.08	-10.15	-8.75	-8.64	-11.25	-8.99	-11.23
4JXX	-8.14	-5.99	-6.05	-6.50	-6.04	-6.24	-6.42	-14.30	-12.02
4JXZ	-8.14	-5.58	-5.61	-6.05	-5.69	-5.76	-5.93	-14.30	-11.57
4LG2	-8.89	-7.96	-8.26	-8.81	-8.03	-8.22	-8.78	-9.33	-10.95
4LJ0	-8.59	-7.80	-7.18	-9.54	-7.21	-7.45	-10.96	-6.28	-8.17

4M7A	-9.70	-8.43	-7.41	-10.99	-8.12	-8.04	-14.48	-9.16	-8.48
4N2Q	-11.45	-8.54	-8.06	-8.57	-8.40	-8.32	-8.62	-10.09	-11.31
4O26	-7.91	-6.82	-6.63	-8.11	-6.99	-6.86	-8.87	-14.83	-10.39
4QEI	-6.55	-4.95	-4.83	-5.11	-4.78	-4.88	-5.60	-13.61	-6.75
4QI2	-9.17	-10.61	-9.48	-15.71	-11.79	-11.51	-23.36	-11.60	-11.32
4R3I	-7.77	-7.29	-7.11	-6.87	-7.18	-6.91	-6.52	-8.72	-9.06
4RCJ	-8.18	-6.32	-7.05	-7.19	-6.41	-6.87	-7.60	-9.45	-8.95
4TUX	-10.41	-8.71	-8.23	-10.13	-8.86	-9.11	-11.35	-10.42	-11.07
4U8T	-9.13	-8.21	-8.34	-13.14	-10.01	-9.20	-16.33	-8.58	-8.24
4WZM	-3.75	-5.30	-5.11	-5.84	-5.13	-5.28	-6.29	-9.74	-10.07
4YVI	-8.67	-5.86	-5.81	-6.29	-5.91	-6.16	-6.29	-13.52	-10.37
4Z31	-8.79	-7.45	-6.98	-8.29	-7.60	-7.52	-9.49	-11.91	-16.22
5DET	-8.11	-5.81	-5.29	-7.31	-5.16	-5.83	-8.65	-9.24	-8.28
5DNO	-7.83	-6.55	-6.22	-6.64	-6.11	-6.25	-7.29	-8.77	-7.31
5ELR	-6.25	-6.94	-7.01	-7.74	-6.95	-7.17	-7.67	-9.25	-9.02
5F5H	-9.18	-8.14	-8.05	-9.58	-9.02	-8.18	-10.73	-9.04	-8.79
5H1K	-7.98	-8.28	-7.74	-9.90	-8.24	-8.01	-10.52	-10.90	-10.26
5H1L	-8.18	-6.98	-6.52	-7.63	-7.52	-7.36	-7.82	-10.47	-10.19
5UDZ	-10.65	-7.84	-7.44	-9.51	-7.99	-8.05	-11.23	-11.95	-8.29
5V7C	-6.99	-7.16	-7.29	-7.63	-7.20	-7.36	-7.31	-9.86	-9.62
5WWW	-6.61	-6.04	-5.94	-6.49	-5.99	-6.13	-6.41	-7.81	-8.36
5WWX	-9.08	-6.43	-6.45	-7.16	-6.46	-6.62	-6.89	-8.47	-8.28
5WZG	-10.05	-7.21	-6.87	-7.82	-7.10	-7.09	-7.95	-9.40	-9.99
5WZK	-9.11	-6.67	-6.37	-7.39	-6.61	-6.47	-7.68	-8.83	-10.17
5X6B	-9.84	-7.48	-7.02	-7.72	-7.19	-7.28	-9.13	-11.89	-16.57
5XJ2	-6.02	-7.04	-7.44	-7.09	-7.07	-7.14	-6.92	DNoA	-9.53
5Y58	-9.42	-8.52	-7.66	-10.97	-8.85	-8.54	-12.75	-15.02	-14.99
5YTV	-8.04	-4.84	-5.11	-5.24	-4.83	-4.97	-5.11	-8.83	-5.93
5Z9X	-4.95	-5.90	-5.90	-6.90	-6.13	-6.49	-7.02	-10.26	-9.49
6CMN	-7.83	-8.02	-7.55	-9.12	-7.65	-7.88	-9.10	-11.66	-7.55
6D12	-9.30	-9.06	-8.79	-11.22	-9.19	-9.23	-12.20	-12.20	-7.85
6DB9	-8.25	-7.66	-7.53	-8.06	-7.57	-7.42	-8.34	-14.90	-10.48
6DCL	-10.65	-8.50	-7.59	-9.35	-7.98	-8.12	-9.75	-9.60	-9.13
6FPQ	-6.93	-7.05	-6.75	-7.26	-7.02	-6.93	-7.99	-8.95	-8.36
6FPX	-9.29	-9.83	-8.88	-14.06	-11.03	-10.51	-18.76	-11.48	-8.49
6FQR	-6.07	-5.04	-5.37	-5.38	-5.22	-5.21	-5.95	-6.46	-8.17
6GX6	-7.26	-4.50	-4.75	-4.79	-4.70	-4.67	-5.21	-7.96	-8.21
6MCE	-10.43	-9.29	-8.56	-10.65	-8.68	-8.94	-11.37	-13.50	-8.38
6MCF	-10.22	-9.87	-9.21	-10.74	-9.46	-9.35	-11.62	-13.50	-10.55
6O16	-10.72	-7.73	-6.82	-10.57	-7.48	-7.14	-12.72	DNoA	-11.95
Total Sample	112	112	112	112	112	112	112	106	107
(r)		**0.63**	**0.59**	**0.53**	**0.59**	**0.59**	**0.44**	**0.18**	**0.18**

Table S5 Example of feature inputs used to train the ML models in this study.

Amino Acid ID	Nucleotide Base ID	Distance (Å)	Local Interaction Energy (kcal/mol)	Hbond Number
ASN	G	9.77	-3.99	2
LYS	A	10.71	-7.62	2
ARG	U	7.76	-8.03	2
GLN	C	8.67	-4.63	3

Table S6 Example of protein-RNA complex 6FPQ (Experimental ΔG = -6.93) to predict the Local energies by the Random Forest model and integrated with local-to-global method to be called as PANTHER score of -7.05.

Amino Acid Number	Amino Acid Name	Nucleotide Base Number	Nucleotide Base Name	Local Energy
336	ASN	5	A	-4.60
336	ASN	6	C	-3.55
338	ARG	6	C	-17.67
352	TYR	3	A	-5.69
392	TYR	4	A	-3.39
406	TYR	3	A	-5.15
436	LYS	3	A	-8.63
437	THR	1	U	-8.04
466	TYR	4	A	-3.37
470	SER	3	A	-3.40
477	ASN	3	A	-5.10
487	ASP	1	U	-4.11
488	ARG	1	U	-18.95
Average				**-7.05**

Table S7. ML-predicted local-to-global score predictions (kcal/mol) of the test set for 30 permutations where distance was randomly shuffled. Columns: PDB code, experimental ΔG, baseline prediction (original features), and 30 permuted predictions (Perm 01 to Perm 30). Each permuted prediction represents the local-to-global decomposed energies after distance perturbation.

TestSet	Exp. ΔG	Baseline-Prediction	Perm01	Perm02	Perm03	Perm04	Perm05	Perm06	Perm07	Perm08	Perm09	Perm10
1EC6	-7.99	-6.03	-5.34	-5.35	-5.43	-5.39	-5.40	-5.40	-5.40	-5.46	-5.37	-5.38
1NYB	-9.13	-7.91	-8.20	-8.22	-8.37	-8.25	-8.27	-8.24	-8.21	-8.45	-8.45	-8.32
1RKJ	-7.99	-7.13	-7.23	-7.27	-7.15	-7.18	-7.16	-7.30	-7.24	-7.24	-7.08	-7.27
1U0B	-8.96	-6.31	-6.33	-6.39	-6.37	-6.37	-6.32	-6.31	-6.36	-6.41	-6.36	-6.37
2B6G	-10.26	-7.59	-7.40	-7.55	-7.48	-7.36	-7.44	-7.46	-7.55	-7.47	-7.39	-7.55
2LBS	-6.09	-5.50	-5.54	-5.54	-5.65	-5.60	-5.52	-5.53	-5.57	-5.64	-5.67	-5.60
2M8D	-8.73	-6.94	-6.53	-6.72	-6.55	-6.51	-6.56	-6.62	-6.58	-6.52	-6.49	-6.50
TestSet	**Exp. ΔG**	**Baseline-Prediction**	**Perm11**	**Perm12**	**Perm13**	**Perm14**	**Perm15**	**Perm16**	**Perm17**	**Perm18**	**Perm19**	**Perm20**
1EC6	-7.99	-6.03	-5.35	-5.35	-5.31	-5.40	-5.31	-5.40	-5.41	-5.42	-5.39	-5.37
1NYB	-9.13	-7.91	-8.28	-8.26	-8.32	-8.20	-8.38	-8.31	-8.28	-8.34	-8.29	-8.29
1RKJ	-7.99	-7.13	-7.21	-7.32	-7.15	-7.25	-7.27	-7.29	-7.23	-7.16	-7.24	-7.29
1U0B	-8.96	-6.31	-6.37	-6.43	-6.38	-6.37	-6.41	-6.36	-6.41	-6.35	-6.36	-6.40
2B6G	-10.26	-7.59	-7.52	-7.41	-7.54	-7.45	-7.35	-7.48	-7.44	-7.51	-7.46	-7.40

2LBS	-6.09	-5.50	-5.58	-5.58	-5.53	-5.63	-5.63	-5.51	-5.58	-5.61	-5.66	-5.61
2M8D	-8.73	-6.94	-6.64	-6.52	-6.61	-6.64	-6.52	-6.55	-6.51	-6.67	-6.55	-6.65
TestSet	**Exp. ΔG**	**Baseline-Prediction**	**Perm21**	**Perm22**	**Perm23**	**Perm24**	**Perm25**	**Perm26**	**Perm27**	**Perm28**	**Perm29**	**Perm30**
1EC6	-7.99	-6.03	-5.37	-5.39	-5.42	-5.28	-5.38	-5.29	-5.30	-5.36	-5.40	-5.46
1NYB	-9.13	-7.91	-8.21	-8.42	-8.27	-8.21	-8.34	-8.28	-8.35	-8.26	-8.29	-8.33
1RKJ	-7.99	-7.13	-7.26	-7.22	-7.19	-7.25	-7.25	-7.26	-7.31	-7.28	-7.22	-7.24
1U0B	-8.96	-6.31	-6.36	-6.30	-6.33	-6.40	-6.36	-6.37	-6.39	-6.34	-6.37	-6.35
2B6G	-10.26	-7.59	-7.54	-7.57	-7.48	-7.46	-7.45	-7.40	-7.57	-7.47	-7.30	-7.39
2LBS	-6.09	-5.50	-5.65	-5.57	-5.63	-5.71	-5.61	-5.64	-5.56	-5.60	-5.76	-5.53
2M8D	-8.73	-6.94	-6.69	-6.66	-6.64	-6.58	-6.55	-6.57	-6.51	-6.57	-6.63	-6.59

Table S8. ML-predicted local-to-global score predictions (kcal/mol) of the test set for 30 permutations where number of Hbond was randomly shuffled. Columns: PDB code, experimental ΔG, baseline prediction (original features), and 30 permuted predictions (Perm 01 to Perm 30). Each permuted prediction represents the local-to-global decomposed energies after Hbond perturbation.

TestSet	**Exp. ΔG**	**Baseline-Prediction**	**Perm01**	**Perm02**	**Perm03**	**Perm04**	**Perm05**	**Perm06**	**Perm07**	**Perm08**	**Perm09**	**Perm10**
1EC6	-7.99	-6.03	-6.20	-6.20	-6.18	-6.23	-6.20	-6.18	-6.23	-6.25	-6.18	-6.20
1NYB	-9.13	-7.91	-7.67	-7.69	-7.67	-7.71	-7.57	-7.60	-7.72	-7.68	-7.71	-7.78
1RKJ	-7.99	-7.13	-6.77	-6.79	-6.74	-6.83	-6.74	-6.74	-6.70	-6.79	-6.70	-6.83
1U0B	-8.96	-6.31	-6.17	-6.18	-6.21	-6.17	-6.16	-6.21	-6.18	-6.21	-6.17	-6.13
2B6G	-10.26	-7.59	-7.06	-7.07	-6.99	-7.02	-7.01	-6.99	-6.98	-7.07	-7.01	-6.96
2LBS	-6.09	-5.50	-5.58	-5.57	-5.65	-5.58	-5.63	-5.60	-5.69	-5.60	-5.66	-5.64
2M8D	-8.73	-6.94	-6.41	-6.29	-6.35	-6.50	-6.51	-6.30	-6.31	-6.30	-6.51	-6.28
TestSet	**Exp. ΔG**	**Baseline-Prediction**	**Perm11**	**Perm12**	**Perm13**	**Perm14**	**Perm15**	**Perm16**	**Perm17**	**Perm18**	**Perm19**	**Perm20**
1EC6	-7.99	-6.03	-6.14	-6.17	-6.18	-6.13	-6.23	-6.19	-6.15	-6.20	-6.22	-6.22
1NYB	-9.13	-7.91	-7.65	-7.67	-7.66	-7.66	-7.57	-7.63	-7.58	-7.65	-7.67	-7.66
1RKJ	-7.99	-7.13	-6.80	-6.78	-6.79	-6.75	-6.77	-6.80	-6.79	-6.80	-6.78	-6.81
1U0B	-8.96	-6.31	-6.21	-6.19	-6.16	-6.18	-6.19	-6.17	-6.17	-6.22	-6.14	-6.20
2B6G	-10.26	-7.59	-7.04	-7.02	-7.01	-7.05	-7.08	-7.06	-7.01	-7.06	-7.04	-7.01
2LBS	-6.09	-5.50	-5.61	-5.68	-5.55	-5.61	-5.64	-5.68	-5.60	-5.58	-5.63	-5.66
2M8D	-8.73	-6.94	-6.38	-6.26	-6.39	-6.33	-6.33	-6.46	-6.29	-6.31	-6.46	-6.30
TestSet	**Exp. ΔG**	**Baseline-Prediction**	**Perm21**	**Perm22**	**Perm23**	**Perm24**	**Perm25**	**Perm26**	**Perm27**	**Perm28**	**Perm29**	**Perm30**
1EC6	-7.99	-6.03	-6.19	-6.18	-6.09	-6.20	-6.24	-6.14	-6.22	-6.14	-6.18	-6.17
1NYB	-9.13	-7.91	-7.64	-7.54	-7.70	-7.65	-7.65	-7.66	-7.65	-7.54	-7.69	-7.80
1RKJ	-7.99	-7.13	-6.77	-6.78	-6.77	-6.80	-6.78	-6.74	-6.78	-6.71	-6.80	-6.78
1U0B	-8.96	-6.31	-6.17	-6.19	-6.23	-6.18	-6.17	-6.23	-6.20	-6.22	-6.20	-6.15
2B6G	-10.26	-7.59	-6.98	-6.98	-6.98	-7.06	-7.01	-7.02	-7.04	-7.07	-6.88	-7.02
2LBS	-6.09	-5.50	-5.63	-5.74	-5.55	-5.60	-5.74	-5.70	-5.66	-5.69	-5.59	-5.60
2M8D	-8.73	-6.94	-6.42	-6.44	-6.33	-6.32	-6.41	-6.36	-6.38	-6.30	-6.33	-6.31

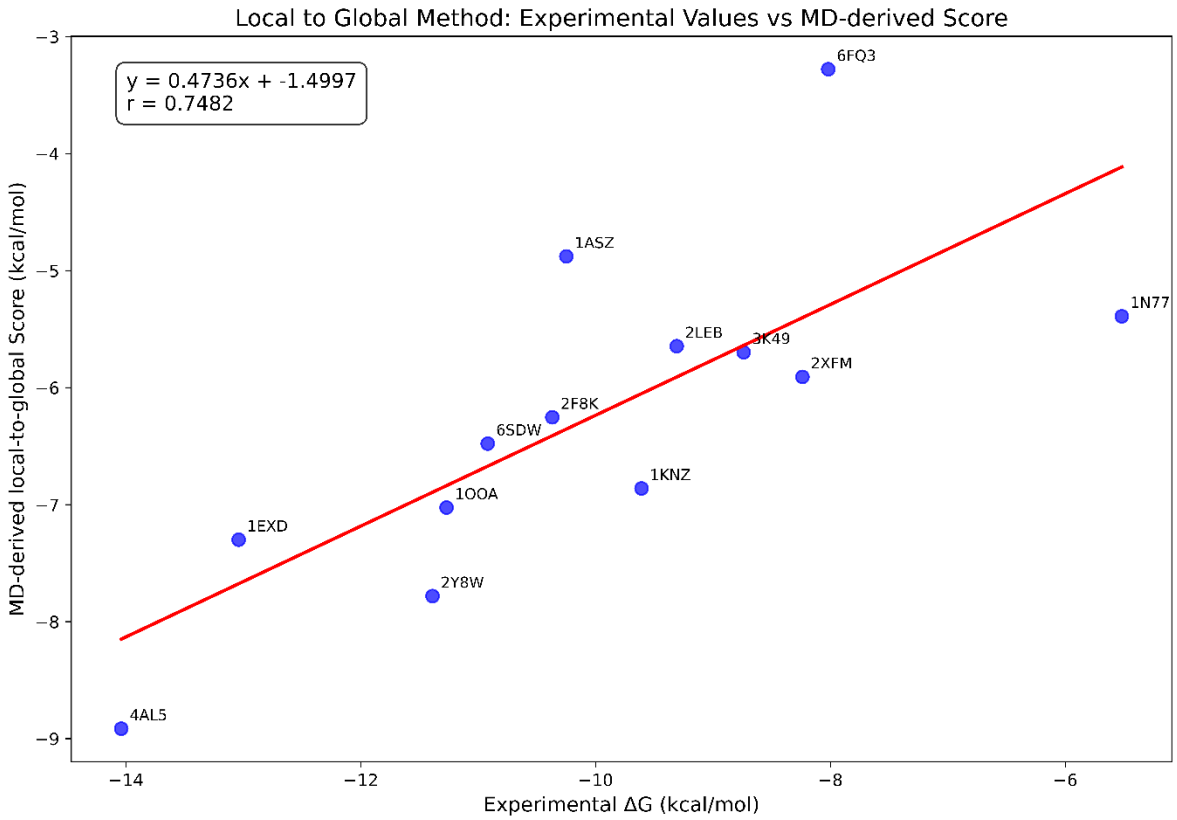

Figure S1. Correlation between the MD-derived score and experimental ΔG values for 13 protein-RNA complexes of train set, showing a Pearson correlation coefficient (r) of 0.75, which confirms the reliability of our fragmental approach.

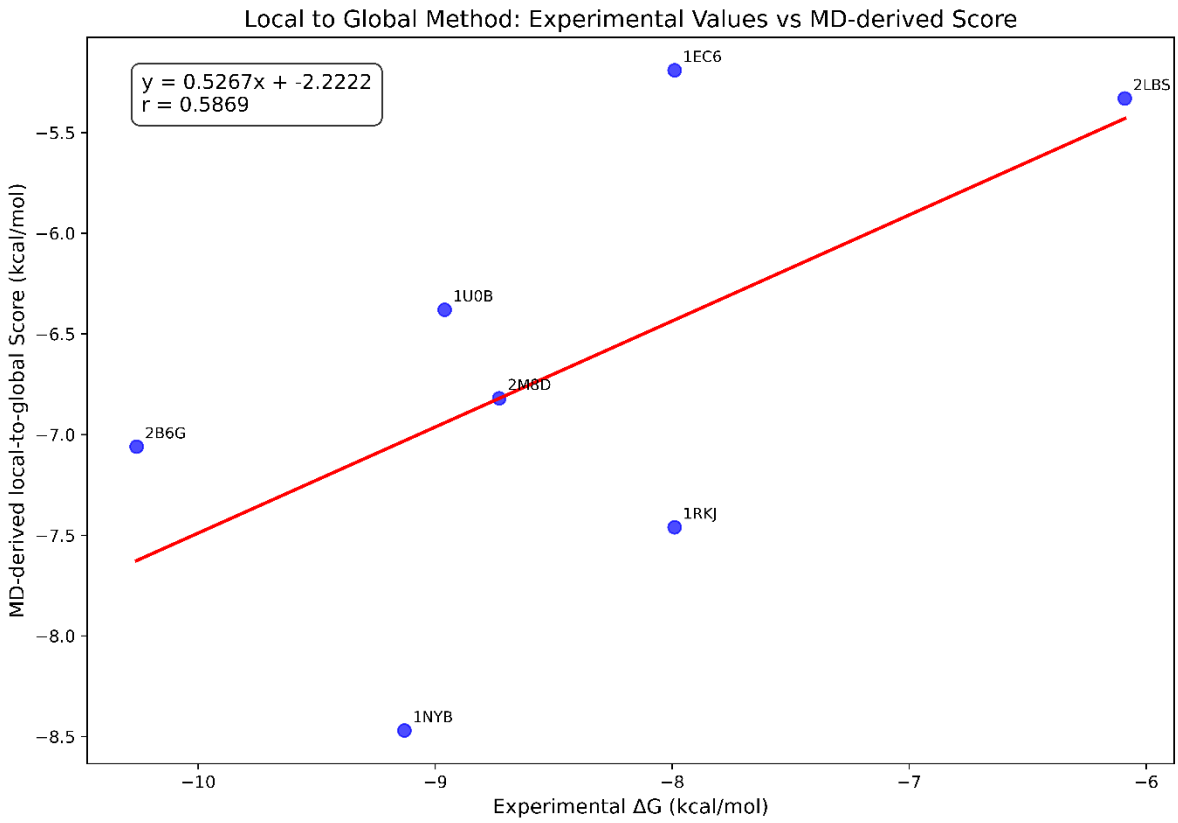

Figure S2. Correlation between the MD-derived local-to-global score and experimental ΔG values for 7 protein-RNA complexes of test set, showing a Pearson correlation coefficient (r) of 0.59, which confirms the reliability of our fragmental approach.

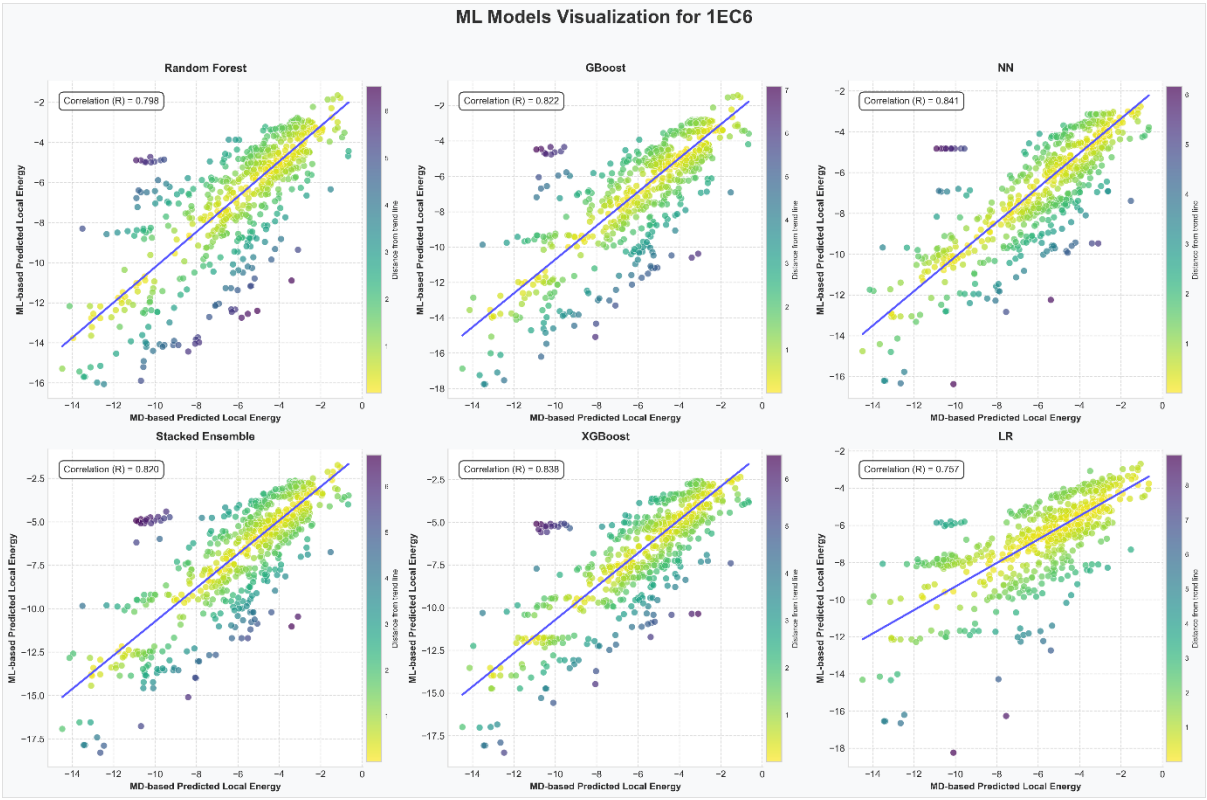

Figure S3. Comparison of MD-derived & ML-derived predicted local energy across six ML models. Points are colored by their distance from the trend line, with similar colors indicating proximity to the correlation line. The correlation coefficient (r) quantifies the agreement between the two prediction methods for each model.

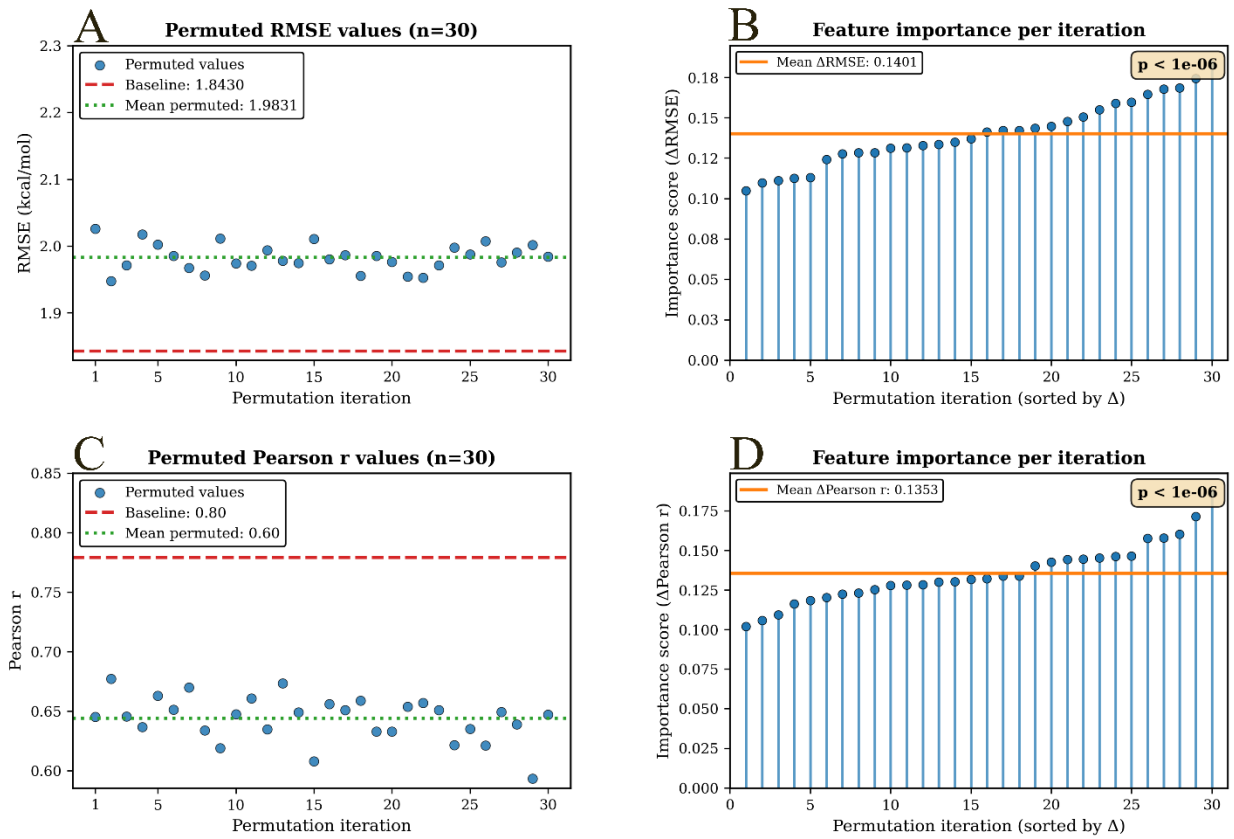

Figure S4. Permutation feature importance analysis for Distance (n = 30 shuffles). A, C: Individual permutation results (blue circles) with the baseline using intact features (red dashed line) and the mean across permutations (green dotted line). B, D: Importance scores with runs sorted by magnitude; the orange line marks the mean. We define ΔRMSE = RMSE_perm − RMSE_base and Δr = r_base − r_perm so larger values indicate greater degradation. Top row: RMSE (kcal/mol). Bottom row: Pearson correlation coefficient. Permuting Distance significantly degrades performance (ΔRMSE = 0.140 ± 0.014 kcal/mol; ΔPearson r = 0.135 ± 0.013; both $p < 10^{-6}$, one-sided t-test; mean ± SD), indicating that intermolecular distance is a critical driver of the model's predictions, consistent with fundamental principles of molecular interaction.

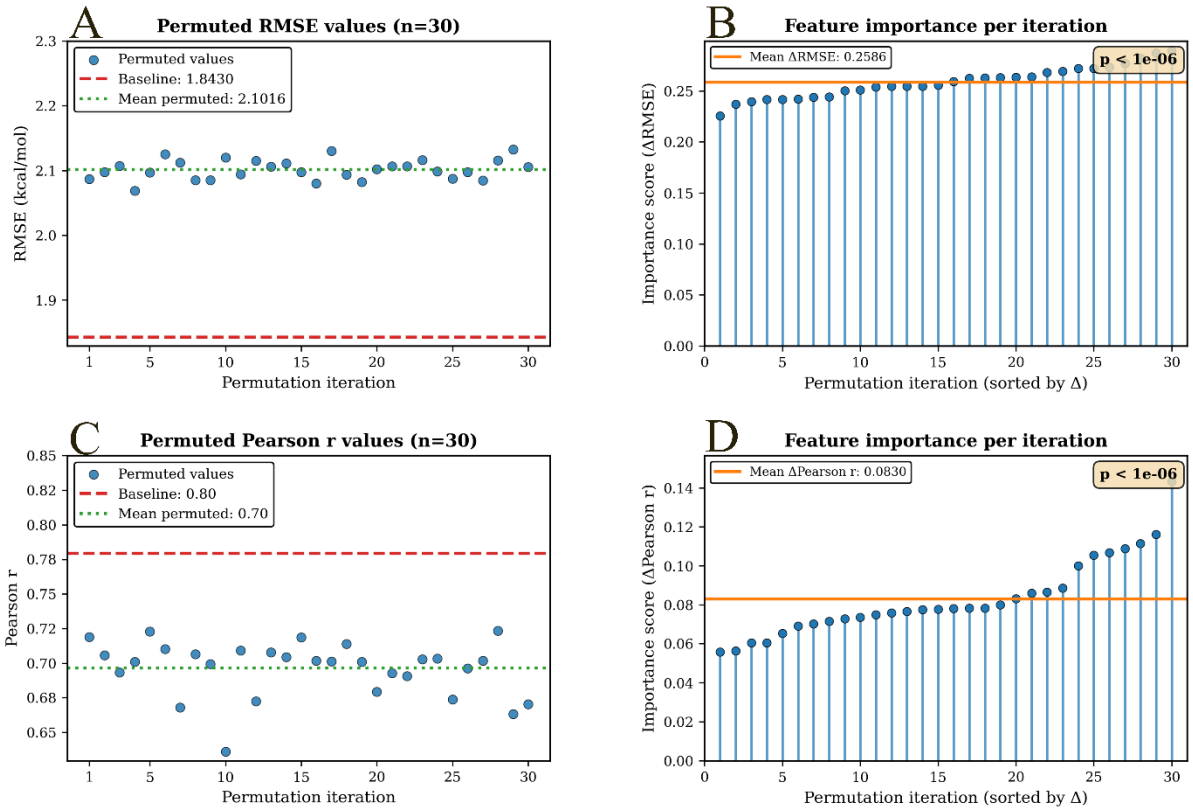

Figure S5. Permutation feature importance analysis for Hbond(num) (n = 30 shuffles), following the same methodology as Figure S1. A, C: Individual permutation results (blue circles) with the baseline using intact features (red dashed) and the mean across permutations (green dotted). B, D: Importance scores with runs sorted by magnitude; the orange line marks the mean. We define ΔRMSE = RMSE_perm − RMSE_base and Δr = r_base − r_perm so larger values indicate greater degradation. Permuting Hbond(num) increased error by ΔRMSE = 0.259 ± 0.007 kcal/mol and reduced correlation by ΔPearson r = 0.083 ± 0.011 (both $p < 10^{-6}$, one-sided t-test; mean ± SD).