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

Supporting Material

SadNet: a novel Multimodal fusion network for protein-ligand binding affinity prediction

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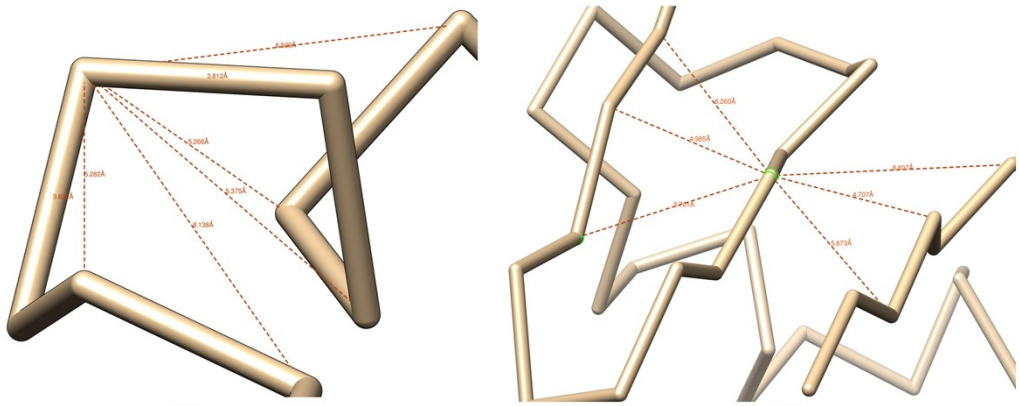

Figure S1 The distance distribution between alpha carbon atoms. Selecting a carbon atom, 8 Angstroms can cover approximately two or three adjacent carbon atoms, as shown in (A). This distance can also cover some atoms in adjacent chains, as shown in (B).

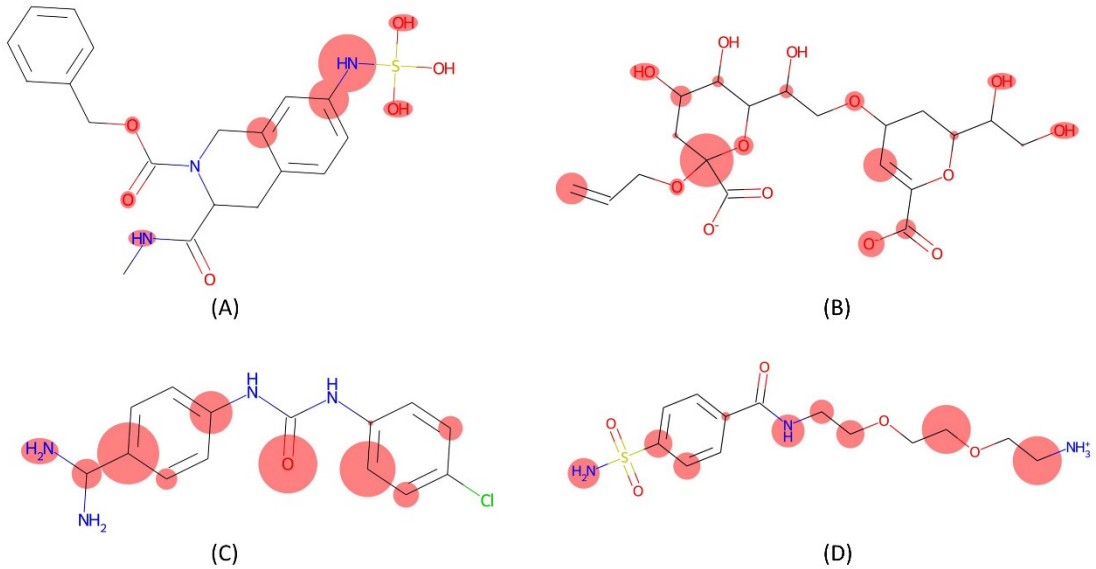

Figure S2 SadNet heat map on (A)2f6v (general-except-refined-set), (B)2r1x (general-except-refined-set), (C)1bju (refined-set), (D)1cnx (refined-set).

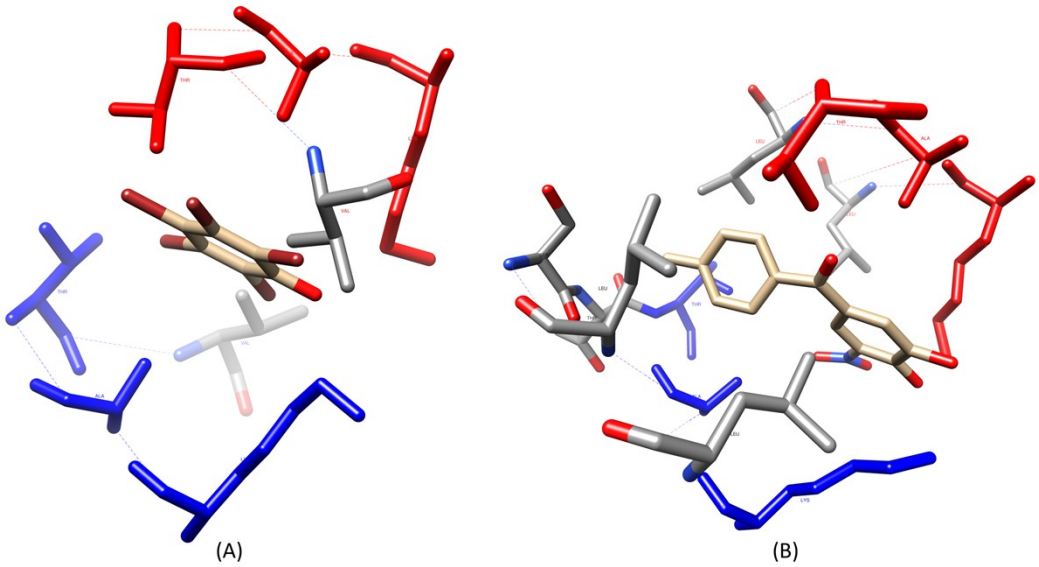

Figure S3 1e4h on the left and 4d7b on the right have the same protein but different ligands. Their pockets also have partially similar amino acids, marked in red and blue.

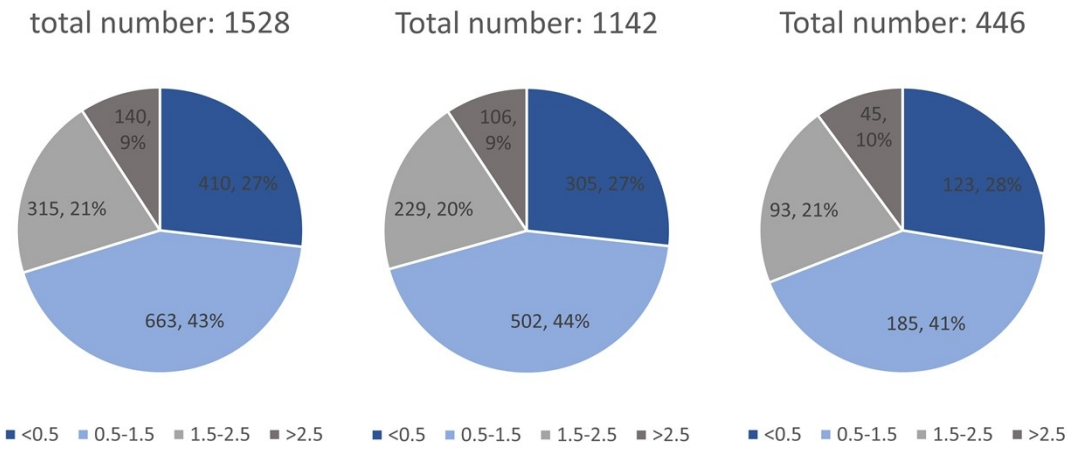

Figure S4 SadNet(R) model performance. From left to right, the samples in the PDBbind2020 extended test set are less similar to the training set. The pie chart shows the distribution of absolute errors between predicted and true values. The proportion of samples less than 0.5 has even increased, proving that the model still has the credibility of prediction.

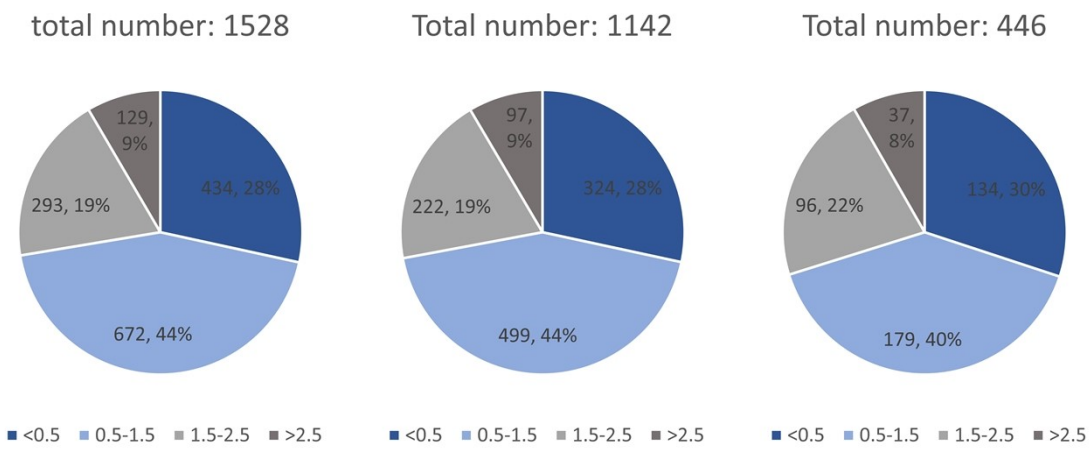

Figure S5 SadNet(G) model performance. From left to right, the samples in the PDBbind2020 extended test set are less similar to the training set. The pie chart shows the distribution of absolute errors between predicted and true values. The proportion of samples less than 0.5 has even increased, proving that the model still has the credibility of prediction.

Table S1 The impact of hyperparameter ***α*** on the Pocket_net

	RMSE	Pearson	MAE
α=0	1.361	0.794	1.112
α=0.3	1.270	0.818	1.004
α=1	1.296	0.805	1.021
α=1.5	1.335	0.792	1.035

α is a hyperparameter in eq5, which can control the proportion of ligand atoms that receive information from the protein chain. Table S1 shows that if ***α*** is too large, Pocket_net will be affected by too much global information and its accuracy will decrease. ***α*** is feasible within 0 to 1. For the purpose of mid-term fusion, which allows the ligand to perceive global information rather than completely covering local information, we select a smaller ***α*** value of 0.3.

Table S2 After losing the protein chain characteristics, the model effect dropped significantly

	RMSE	Pearson	MAE
Seq_net	1.332	0.790	1.036
Seq_net (ligand only)	1.612	0.671	1.300

Table S3 Graph neural network layer analysis

Model	Number of layers	RMSE	Pearson	MAE
Pocket_net	2	1.405 (0.018)	0.770 (0.009)	1.109 (0.005)
	3	1.281 (0.019)	0.811 (0.006)	1.016 (0.009)
	4	1.324 (0.032)	0.798 (0.010)	1.042 (0.034)
	5	1.407 (0.031)	0.766 (0.012)	1.113 (0.030)
Seq_net	2	1.358 (0.011)	0.782 (0.004)	1.061 (0.017)
	3	1.347 (0.015)	0.787 (0.006)	1.057 (0.014)
	4	1.370 (0.019)	0.777 (0.006)	1.069 (0.013)
	5	1.421 (0.014)	0.758 (0.005)	1.124 (0.014)

Table S4 Average results of 5 random seed trainings of SadNet and submodels

	RMSE	Pearson	MAE
Pocket_net (no virtual node)	1.347 (0.024)	0.794 (0.011)	1.071 (0.023)
Pocket_net	1.281 (0.019)	0.811 (0.006)	1.016 (0.009)
Seq_net	1.347 (0.015)	0.787 (0.006)	1.057 (0.014)
SadNet	1.249 (0.005)	0.822 (0.002)	0.991 (0.009)

SadNet is trained using the intermediate features of pocket_net (RMSE=1.270, Pearson=0.818, MAE=1.004) and seq_net (RMSE=1.332, Pearson=0.790, MAE=1.036). When the learning rate is 0.00005, stable convergence can be achieved.