FABind: Fast and Accurate Protein-Ligand Binding

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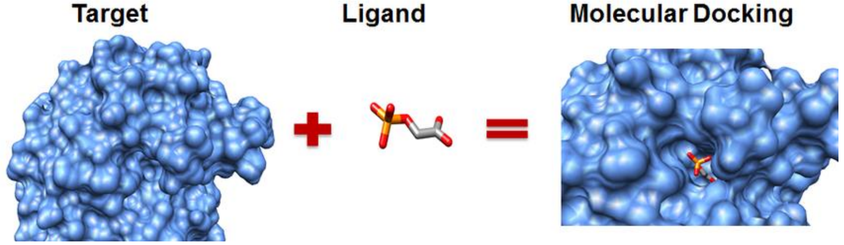
Project Page

NEURAL INFORMATION PROCESSING SYSTEMS

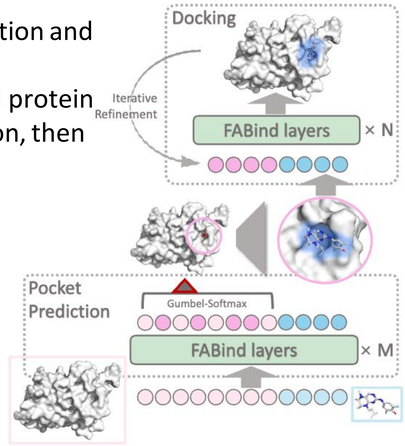
Protein-ligand binding/docking is crucial for drug discovery

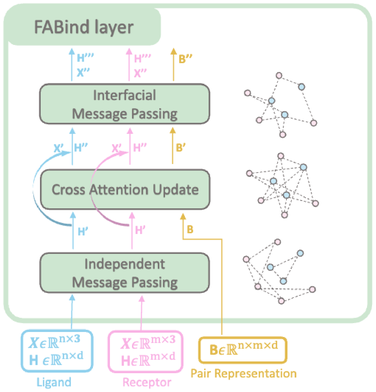


- **Sampling-based method**: accurate, but requires large space of sampling candidates, scoring function learning
  → High cost and low speed
- **Regression-based method**: fast, directly predict the docking pose.
  → Accuracy is not as good as sampling method

FABind: fast and accurate protein-ligand binding

- **Unified network** for pocket prediction and docking process
- **End-to-end framework**, input rigid protein and random molecule conformation, then output the predicted pose
- **Scheduled sampling**, training with predicted pocket





- Independent message passing: inside protein and molecule
- Cross-attention update: cross protein and molecule
- Interfacial message passing: on the protein-molecule contact surface

Pocket prediction

- **Pocket classification**

$$L_p^c = -\frac{1}{n_p}\sum_{j=1}^{n_p}[y_j \log(p_j) + (1-y_j)\log(1-p_j)]$$

- **Constraint for pocket center coordinates**

$$\gamma_j^p = \frac{\exp((\log(p_j)+g_j)/\tau_e}{\sum_{k'=1}^{n_p}\exp(\log(p_{k'})+g_{k'})/\tau_e}, \quad x^p = \frac{1}{n_p}\sum_{j=1}^{n^p}\gamma_j^p x_j^p$$

$$L_p^{c2r} = l_{Huber}(x^p, x^{p*})$$

$$L_{pocket} = L_p^c + \alpha L_p^{c2r}$$

Docking

- **Direct coordinates prediction**

$$L_{coord} = l_{Huber}(x^L, x^*)$$

- **Constraint by distance matrix**

$$\widetilde{D_{ij}} = \|x_i^L - x_j^L\|, \qquad \widehat{D_{ij}} = MLP(z_{ij}^L)$$

$$L_{dist} = \frac{1}{n^l n^{p*}}\{\sum\sum[(D_{ij}-\widetilde{D_{ij}})^2 + (D_{ij}-\widehat{D_{ij}})^2 + \gamma(\widetilde{D_{ij}}-\widehat{D_{ij}})^2]\}$$

$$L_{docking} = L_{coord} + \beta L_{dist}$$

Comprehensive loss for joint optimization

$$L = L_{pocket} + L_{docking}$$

Experimental results

- Blind self-docking performance on the **whole test set**

Methods	Ligand RMSD Percentiles ↓ 25%	50%	75%	Mean	% Below ↑ 2Å	5Å	Centroid Distance Percentiles ↓ 25%	50%	75%	Mean	% Below ↑ 2Å	5Å	Average Runtime (s)
QVINA-W	2.5	7.7	23.7	13.6	20.9	40.2	0.9	3.7	22.9	11.9	41.0	54.6	49*
GNINA	2.8	8.7	22.1	13.3	21.2	37.1	1.0	4.5	21.2	11.5	36.0	52.0	146
SMINA	3.8	8.1	17.9	12.1	13.5	33.9	1.3	3.7	16.2	9.8	38.0	55.9	146*
GLIDE	2.6	9.3	28.1	16.2	21.8	33.6	0.8	5.6	26.9	14.4	36.1	48.7	1405*
VINA	5.7	10.7	21.4	14.7	5.5	21.2	1.9	6.2	20.1	12.1	26.5	47.1	205*
EQUIBIND	3.8	6.2	10.3	8.2	5.5	39.1	1.3	2.6	7.4	5.6	40.0	67.5	**0.03**
TANKBIND	2.6	4.2	7.6	7.8	17.6	57.8	0.8	1.7	4.3	5.9	55.0	77.8	0.87
E3BIND	2.1	3.8	7.8	7.2	23.4	60.0	0.8	1.5	4.0	5.1	60.0	78.8	0.44
DIFFDOCK (1)	2.4	4.9	8.9	8.3	20.4	51.0	0.7	1.8	4.5	5.8	54.1	76.8	2.72
DIFFDOCK (10)	1.6	3.8	7.9	7.4	32.4	59.7	0.6	1.4	3.6	5.2	60.7	79.8	20.81
DIFFDOCK (40)	**1.5**	3.5	7.4	7.4	**36.0**	61.7	**0.5**	**1.2**	**3.3**	5.4	**62.9**	**80.2**	82.83
FABIND	1.7	**3.1**	**6.7**	**6.4**	33.1	**64.2**	0.7	1.3	3.6	**4.7**	60.3	**80.2**	0.12

- Blind self-docking performance on the **unseen receptors**

Methods	Ligand RMSD Percentiles ↓ 25%	50%	75%	Mean	% Below ↑ 2Å	5Å	Centroid Distance Percentiles ↓ 25%	50%	75%	Mean	% Below ↑ 2Å	5Å	Average Runtime (s)
QVINA-W	3.4	10.3	28.1	16.9	15.3	31.9	1.3	6.5	26.8	15.2	35.4	47.9	49*
GNINA	4.5	13.4	27.8	16.7	13.9	27.8	2.0	10.1	27.0	15.1	25.7	39.5	146
SMINA	4.8	10.9	26.0	15.7	9.0	25.7	1.6	6.5	25.7	13.6	29.9	41.7	146*
GLIDE	3.4	18.0	31.4	19.6	**19.6**	28.7	1.1	17.6	29.1	18.1	29.4	40.6	1405*
VINA	7.9	16.6	27.1	18.7	1.4	12.0	2.4	15.7	26.2	16.1	20.4	37.3	205*
EQUIBIND	5.9	9.1	14.3	11.3	0.7	18.8	2.6	6.3	12.9	8.9	16.7	43.8	**0.03**
TANKBIND	3.4	5.7	10.8	10.5	3.5	43.7	1.2	2.6	8.4	8.2	40.9	70.8	0.87
E3BIND	3.0	6.1	10.2	10.1	6.3	38.9	1.2	2.3	7.0	7.6	43.8	66.0	0.44
DIFFDOCK (1)	4.1	7.2	18.2	12.5	8.1	33.1	1.4	3.7	16.7	10.0	33.6	58.3	2.72
DIFFDOCK (10)	3.2	6.4	16.5	11.8	14.2	38.7	1.1	2.8	13.3	9.3	39.7	62.6	20.81
DIFFDOCK (40)	2.8	6.4	16.3	12.0	17.2	42.3	1.0	2.7	14.2	9.8	43.3	62.6	82.83
FABIND	**2.2**	**3.4**	**8.3**	**7.7**	**19.4**	**60.4**	**0.9**	**1.5**	**4.7**	**5.9**	**57.6**	**75.7**	0.12

- Blind self-docking performance on Apo proteins

Method	Apo ESMFold proteins Top-1 RMSD %<2	Med.
GNINA	2.0	22.3
SMINA	3.4	15.4
EQUIBIND	1.7	7.1
TANKBIND	10.4	5.4
P2RANK+SMINA	4.6	10.0
P2RANK+GNINA	8.6	11.2
EQUIBIND+SMINA	4.3	8.3
EQUIBIND+GNINA	10.2	8.8
DIFFDOCK (10)	21.7	5.0
DIFFDOCK (40)	20.3	5.1
FABIND	**24.9**	**4.2**

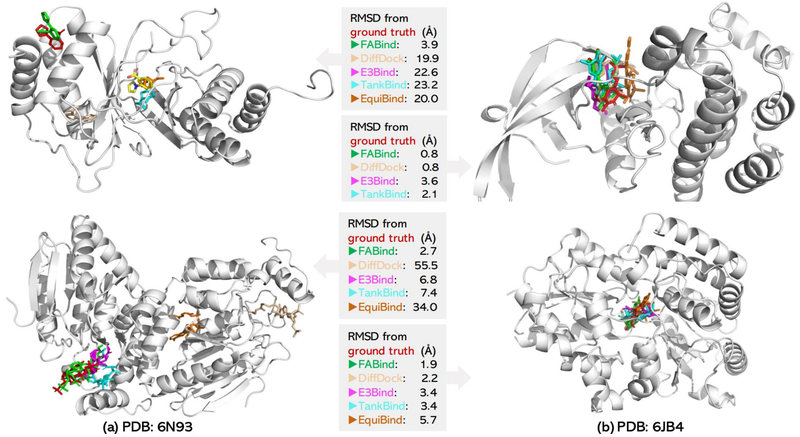
- **Pocket prediction** performance

Methods	DCC % Below ↑ 3Å	4Å	5Å
TANKBIND	18.2	32.0	39.9
E3BIND	26.7	35.8	50.1
P2RANK	36.4	50.1	57.0
FABIND	**42.7**	**56.5**	**62.8**
- LIGAND INFORMATION	36.9	51.5	59.0
- CENTER CONSTRAINT	8.8	22.9	31.7

- Ablation study

Methods	RMSD Mean (Å)↓	RMSD % Below 2Å↑
FABIND	6.4	33.1
NO SCHEDULED SAMPLING	6.4	28.7
COORD LOSS ONLY	6.9	16.3
NO ITERATIVE REFINEMENT	6.6	22.5
NO CROSS-ATTENTION	6.4	21.4

- Cases demonstration



(a) PDB: 6N93 (b) PDB: 6JB4