

# **Molecular Property Prediction**

MolProPred

Apr. 2023

### Outline

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- Message-Passing functions
- Readout

#### Molecular GNN

- 1D String
- 2D Graphs
- 3D Euclidean Space

#### SchNet Algorithm

#### SchNet for Scalar Coupling

- Main result & issues
- Tests
- Score & Rank

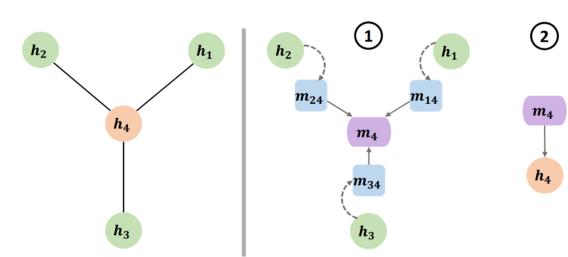
## Message-Passing GNN

#### (a) Initialization

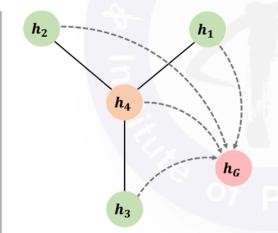
G=(V, E), *i*-th node  $u_i \in V$ , edge  $e_{i,j} \in E$ .

 $u_i$  initialized as  $\mathbf{h}_i^{(0)} = \operatorname{Emb}_n(u_i)$ 

 $e_{i,j}$  initialized as  $\mathbf{a}_{ij} = \operatorname{Emb}_e(e_{ij})$ 



- (a) An example graph
- (b) Message-passing function



(c) Readout function

## Message-Passing GNN

#### (b) Message-passing function

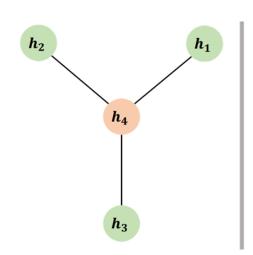
① Aggregate:

$$\mathbf{m}_i^{(k)} = \sum_{u_j \in \operatorname{N}\left(u_i
ight)} \phi_m^{(k)}\left(\mathbf{h}_i^{(k-1)}, \mathbf{h}_j^{(k-1)}, \mathbf{a}_{ij}
ight)$$

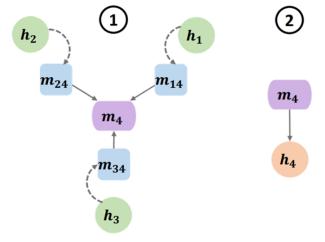
② Update (transformer):

$$\mathbf{h}_i^{(k)} \! = \! \phi_u^{(k)} \! = \! \left( \mathbf{h}_i^{(k-1)}, \! \mathbf{m}_i^{(k)} 
ight)$$

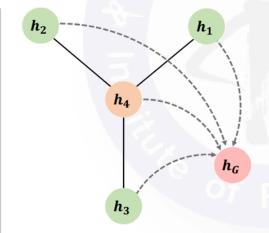
 $\phi_m^{(k)}(\cdot), \phi_u^{(k)}(\cdot)$ : message/update functions.



(a) An example graph



(b) Message-passing function



(c) Readout function

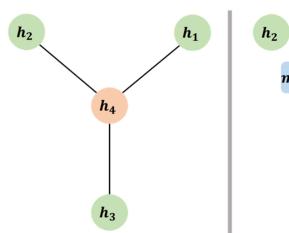
## Message-Passing GNN

#### (c) Readout operations

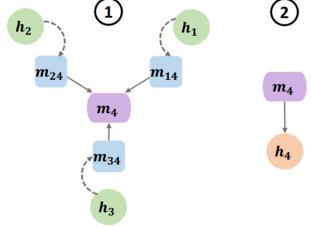
After the last message-passing layer:

$$\mathbf{h}_G = R(\{\mathbf{h}_i^{(k)} \mid u_i \in \mathbf{V}\})$$

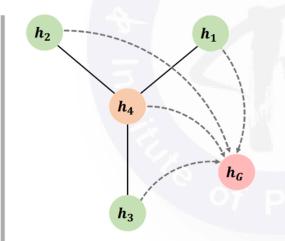
 $R(\cdot)$ : readout function.



(a) An example graph



(b) Message-passing function



(c) Readout function

### Molecular GNN

#### 1D string:

- SMILES, SMARTS, SELFIES, ECFP, MACCS, . . .
- Struggle to directly model topological and geometric information.

2D graph: only topological info.

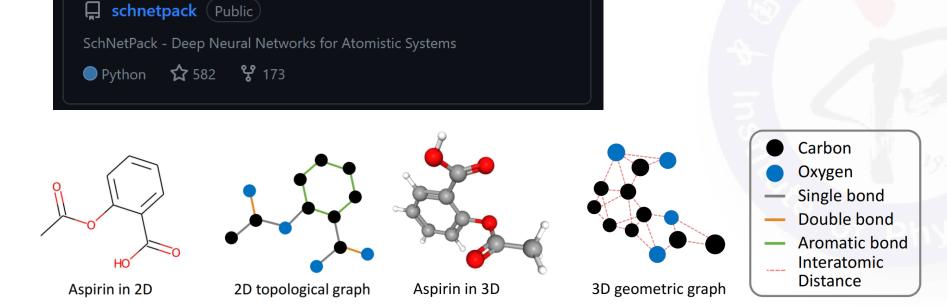
- Duvenaud et al., Hu et al., MPNN, . . .
- Ignore distance and angle information.



### Molecular GNN

#### GNNs for molecules in 3D Euclidean space:

- Deep tensor neural network (DTNN): model distance in messagepassing.
- **SchNet**: well designed layers to model local correlations, effectively encodes 3D distance to GNN, and inspires many follow-up works.



#### SchNet - Introduction



SchNet: model atomistic systems by making use of continuous-filter convolutional layers(model interaction between atoms).



Allow to model complex atomic interactions.

Predict potential energy surfaces.

Speed up the exploration of chemical space.

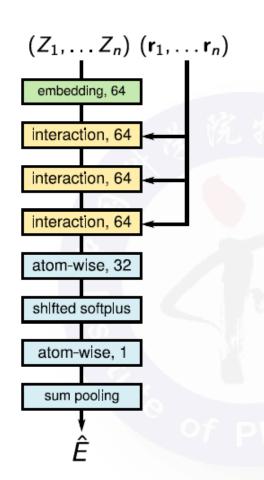


Consider fundamental symmetries of atomistic systems.

rotational and translational invariance as well as invariance to atom indexing

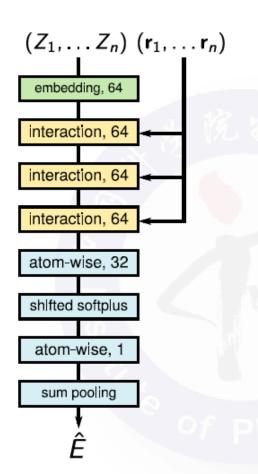
### Method

- SchNet is a variant of the earlier proposed Deep Tensor Neural Networks(DTNN).
  - DTNN: interactions are modeled by tensor layers, i.e., atom representations and interatomic distances are combined using a parameter tensor.
  - SchNet: makes use of continuous-filter convolutions with filter-generating networks to model the interaction term.



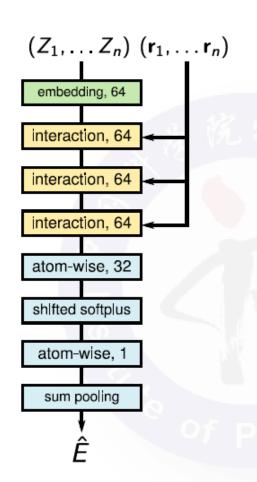
### Method

- ➤ At each layer, the molecule is represented atom-wise analogous to pixels in an image.
- Interactions between atoms are modeled by the three interaction blocks.
- ➤ The final prediction is obtained after atomwise updates of the feature representation and pooling of the resulting atom-wise energy.



## Molecular representation

- $\triangleright$  Nuclear charges  $Z=(Z_1,...,Z_n)$
- $\triangleright$  Positions R=( $\mathbf{r}_1,...,\mathbf{r}_n$ )
- The atoms are described by a tuple of features  $X' = (\mathbf{x}_1', ..., \mathbf{x}_n')$ 
  - $\mathbf{x}_i' \in \mathbb{R}^F$  F: number of feature maps
  - n: number of atoms
  - I: current layer
- $\mathbf{x}_{i}^{0}$  is initialized using an embedding dependent on the atom type  $\mathbf{Z}_{i}$ .  $\mathbf{x}_{i}^{0} = \mathbf{a}_{Z_{i}}$
- $\triangleright$  The atom type embeddings  $\mathbf{a}_{\mathbb{Z}}$  are initialized randomly and optimized during training.

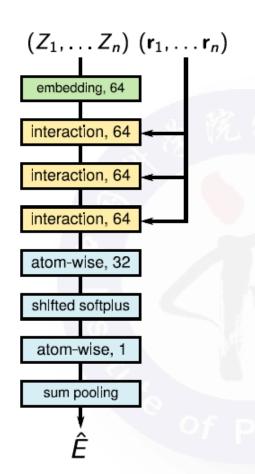


## Atom-wise layers

- Are dense layers.
- Applied separately to the representations x<sub>i</sub> of each atom i:

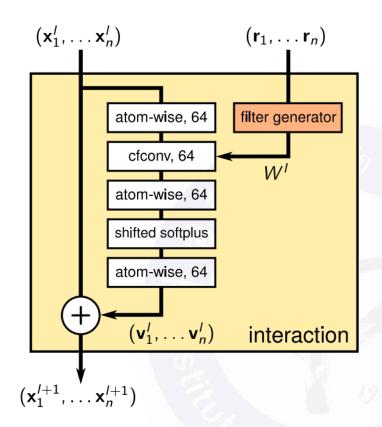
$$\mathbf{x}_i^{l+1} = W^l \mathbf{x}_i^l + \mathbf{b}^l$$

- Weights W<sup>1</sup> and biases b<sup>1</sup> are shared across atoms.
- The architecture remains scalable with respect to the number of atoms.
- ➤ These layers are responsible for the recombination of feature maps.



### Interaction blocks

- Updating the atomic representations based on pair-wise interactions with the surrounding atoms.
- Continuous-filter convolutional layers, a generalization of the discrete convolutional layers commonly used.
  - Atoms are located at arbitrary positions.
- Model the filters continuously with a filter-generation neural network W that maps the atom positions to the corresponding values of the filter bank.

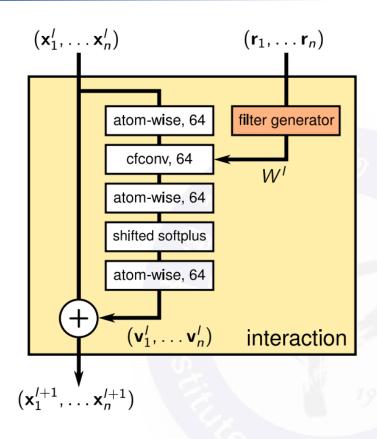


$$egin{align} \mathbf{x}_i^{l+1} &= \left(X^{l} * W^l
ight)_i \ &= \mathbf{x}_j^l \circ W^l (\mathbf{r}_j - \mathbf{r}_i) \end{split}$$

### Interaction blocks

Activation functions: shifted softplus  $ssp(x)=ln(0.5 e^x+0.5)$ 

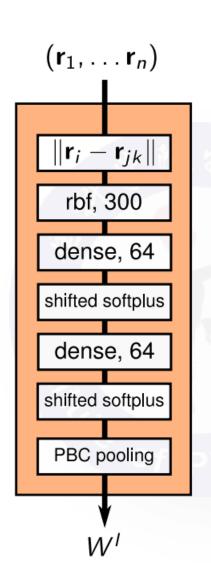
- ssp(0) = 0.
- Improves the convergence of the network while having infinite order of continuity.
- Obtain
  - smooth potential energy surfaces.
  - force fields.
  - second derivatives that are required for training with forces as well as the calculation of vibrational modes.



# Filter-generating networks

- Determines how interactions between atoms are modeled.
- Constrain the model and include chemical knowledge.
- ➤ Input: a fully-connected neural network that takes the vector pointing from atom *i* to its neighbor *j*.
- Rotationally invariant: requirements for modeling molecular energies. Obtained by using interatomic distances:

$$d_{ij} = \|\mathbf{r}_i - \mathbf{r}_j\|$$



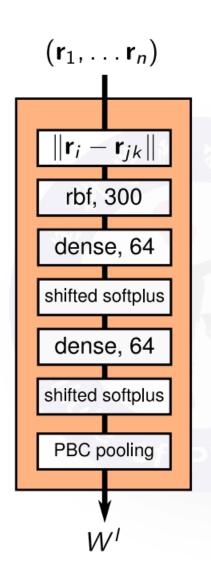
## Filter-generating networks

#### Rotationally invariant

- Filters would be highly correlated: a neural network after initialization is close to linear.
- > Expand the distances in a basis of Gaussians:

$$e_k(\mathbf{r}_i - \mathbf{r}_j) = \exp\left[-\gamma(\|\mathbf{r}_i - \mathbf{r}_j\| - \mu_k)^2\right]$$

- $\succ \mu_k$ : chosen on a uniform grid between zero and the distance cutoff.
- The number of Gaussians and the hyper parameter y determine the resolution of the filter.



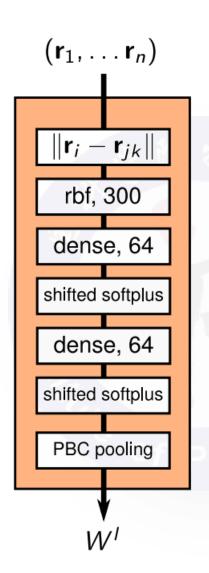
## Filter-generating networks

#### Periodic boundary conditions

- $\succ$  Each atom-wise feature vector  $\mathbf{x}_i$  has to be equivalent across all periodic repetitions.
- > Given a filter  $\tilde{W}^l(\mathbf{r}_{jb} \mathbf{r}_{ia})$  a,b: unit cell over all atoms with  $\|\mathbf{r}_{jb} \mathbf{r}_{ia}\| < r_{\mathrm{cut}}$ .

$$egin{aligned} \mathbf{x}_i^{l+1} &= \mathbf{x}_{im}^{l+1} = rac{1}{n_{ ext{neighbors}}} \sum_{j,n} \mathbf{x}_{jn}^l \circ ilde{W}^l (\mathbf{r}_{jn} - \mathbf{r}_{im}) \ &= rac{1}{n_{ ext{neighbors}}} \sum_{j} \mathbf{x}_j^l \circ \left( \sum_{n} ilde{W}^l (\mathbf{r}_{jn} - \mathbf{r}_{im}) 
ight) \end{aligned}$$

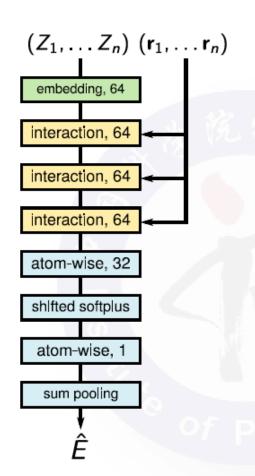
More stable when normalizing the filter response  $\mathbf{x}_{i}^{l+1}$  by the number of atoms within the cutoff range.



## Property prediction

- ightharpoonup Compute atom-wise contributions  $\hat{P}_i$  from the fully-connected prediction network.
- $\triangleright$  Calculate the final prediction  $\widehat{P}$  by summing (intensive) or averaging (extensive) over the atomic contributions, respectively.
- ➤ As SchNet yields rotationally invariant energy predictions, the force predictions are rotationally equivariant by construction.
- Predicting atomic forces:

$$\hat{\mathbf{F}}_i(Z_1,...,\!Z_n,\!\mathbf{r}_1,...,\!\mathbf{r}_n) = -\,rac{\partial \hat{E}}{\partial \mathbf{r}_i}(Z_1,...,\!Z_n,\!\mathbf{r}_1,...,\!\mathbf{r}_n)$$



## Training

Train SchNet for each property target P by minimizing the squared loss:

$$\ell(\hat{P}, P) = \left\| P - \hat{P} \right\|^2$$

Train energies and forces with combined loss:

$$\ell\left(\left(\hat{E},\mathbf{F}_{1},\ldots,\mathbf{F}_{n}\right)\right),\left(E,\mathbf{F}_{1},\ldots,\mathbf{F}_{n}\right)=\rho\left\|E-\hat{E}\right\|^{2}+\frac{1}{n_{\text{atoms}}}\sum_{i=0}^{n_{\text{atoms}}}\left\|\mathbf{F}_{i}-\left(-\frac{\partial\hat{E}}{\partial\mathbf{R}_{i}}\right)\right\|^{2}$$

- ρ: trade-off between energy and force loss.
- In each experiment, we split the data into a training set of given size N and use a validation set for early stopping.
- Remaining data is used for computing the test errors.

# Kaggle: predict scalar coupling constant

#### **Coupling Tensor**

#### **Scalar Coupling Constant**

$$\ddot{J}_{KL} = h \frac{\gamma_K}{2\pi} \frac{\gamma_L}{2\pi} \frac{d^2 E}{d\mathbf{M}_K d\mathbf{M}_L} \qquad J_{KL} = \frac{1}{3} \text{Tr} \ddot{J}_{KL}$$



$$J_{KL} = \frac{1}{3} \text{Tr} \ddot{J}_{KL}$$

Electronic Energy  $E(\mathbf{M}_K, \mathbf{M}_L; \lambda_S, \lambda_T)$ 

Quantum **Mechanics** 

$$\frac{d^2E}{d\mathbf{M}_K d\mathbf{M}_L} = \frac{\partial^2 E}{\partial \mathbf{M}_K \partial \mathbf{M}_L} + \frac{\partial^2 E}{\partial \mathbf{M}_K \partial \lambda_S} \frac{\partial \lambda_S}{\partial \mathbf{M}_L} + \frac{\partial^2 E}{\partial \mathbf{M}_K \partial \lambda_T} \frac{\partial \lambda_T}{\partial \mathbf{M}_L}$$

DSO PSO FC+SD **Ground State** Singlet and Triplet **Excited States** 

**SchNet** 

$$\frac{d^2E}{d\mathbf{M}_K d\mathbf{M}_L} = \sum_{i=1}^n \frac{d^2e_i}{d\mathbf{M}_K d\mathbf{M}_L} = \sum_{i=1}^n \ddot{\zeta}_i$$

https://www.kaggle.com/competitions/champs-scalar-coupling/discussion/106424

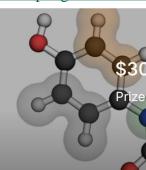


#### **Predicting Molecular Properties**

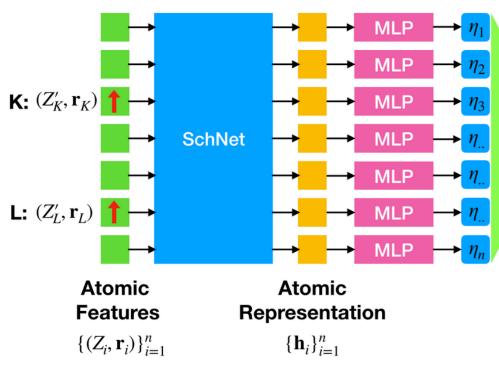
Can you measure the magnetic interactions between a pair of atoms?



CHAMPS (CHemistry And Mathematics in Phase Space) 2,737 teams 4 years ago



# Kaggle: predict scalar coupling constant



Scalar Coupling Constant

$$J_{KL} = \sum_{i} \eta_{i}$$

$$\eta_i = h \frac{\gamma_K}{2\pi} \frac{\gamma_L}{2\pi} \frac{1}{3} \text{Tr} \ddot{\zeta}_i$$

https://www.kaggle.com/competitions/champs-scalar-coupling/discussion/106424



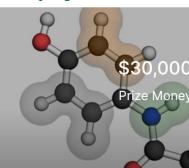
Featured Prediction Competition

#### **Predicting Molecular Properties**

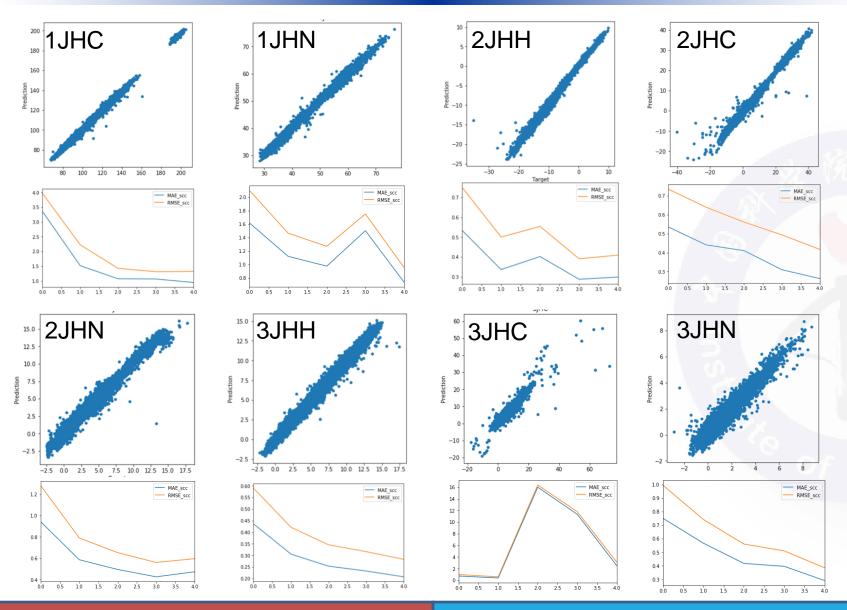
Can you measure the magnetic interactions between a pair of atoms?



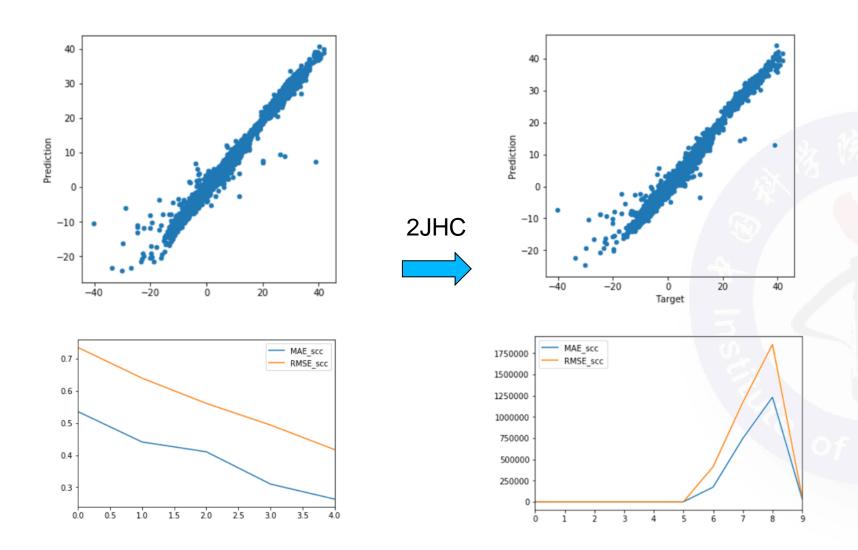
CHAMPS (CHemistry And Mathematics in Phase Space)  $\,\cdot\,$  2,737 teams  $\,\cdot\,$  4 years ago



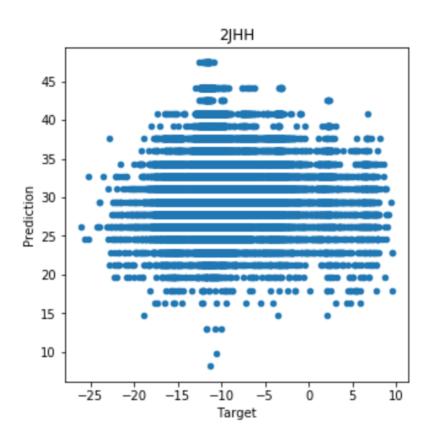
### Result



# Test: increase epoch steps to 10

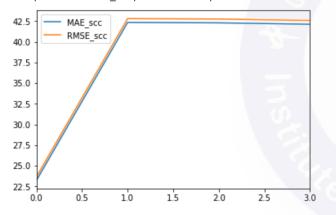


## Test: increase learning rate (3 epochs)



	Time	Learning rate	Train loss	Validation loss	MAE_scc	RMSE_scc
0	405.813638	0.01	4.721478e+12	559.274815	23.224133	23.648992
1	814.477964	0.01	9.940983e+18	1832.295706	42.347378	42.805323
2	1224.116501	0.01	4.320177e+06	1827.820094	42.295350	42.753013
3	1635.426513	0.01	4.299901e+06	1813.133102	42.124165	42.580901

<matplotlib.axes.\_subplots.AxesSubplot at 0x7ade7efdd2e8>

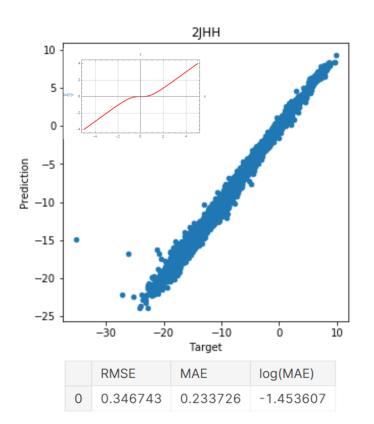


## Test: change activation function

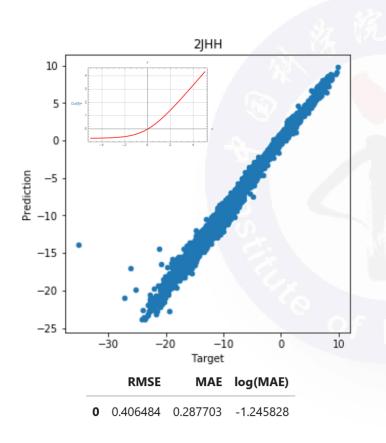
#### TORCH.NN.FUNCTIONAL.TANHSHRINK

torch.nn.functional.tanhshrink(input)  $\rightarrow$  Tensor [SOURCE]

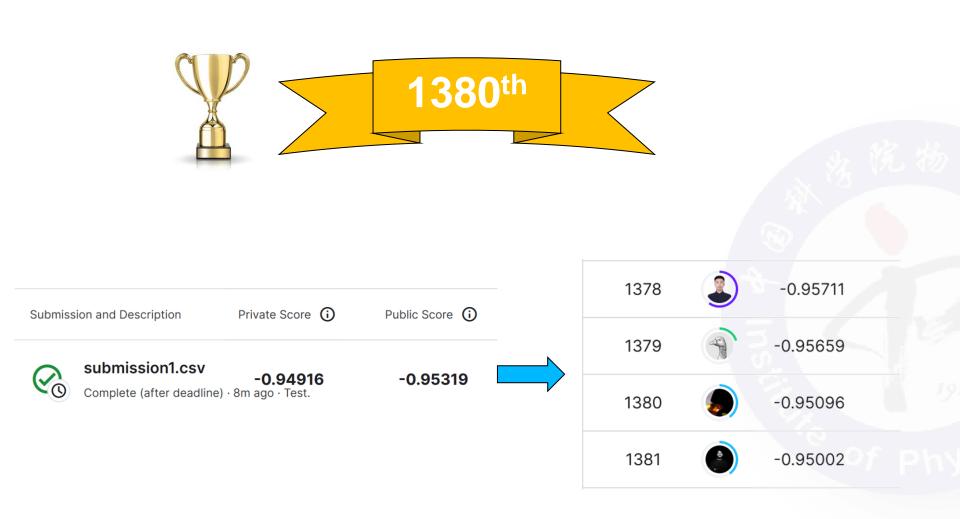
Applies element-wise,  $\operatorname{Tanhshrink}(x) = x - \operatorname{Tanh}(x)$ 



Default:  $ssp(x) = ln(0.5 e^x + 0.5)$ 



### Score & Rank



Repo: <a href="https://github.com/InterStellarAlice/MolProPred">https://github.com/InterStellarAlice/MolProPred</a>

# THANKS!