# Molecular Property Prediction

MolProPred

Apr. 2023

# Outline

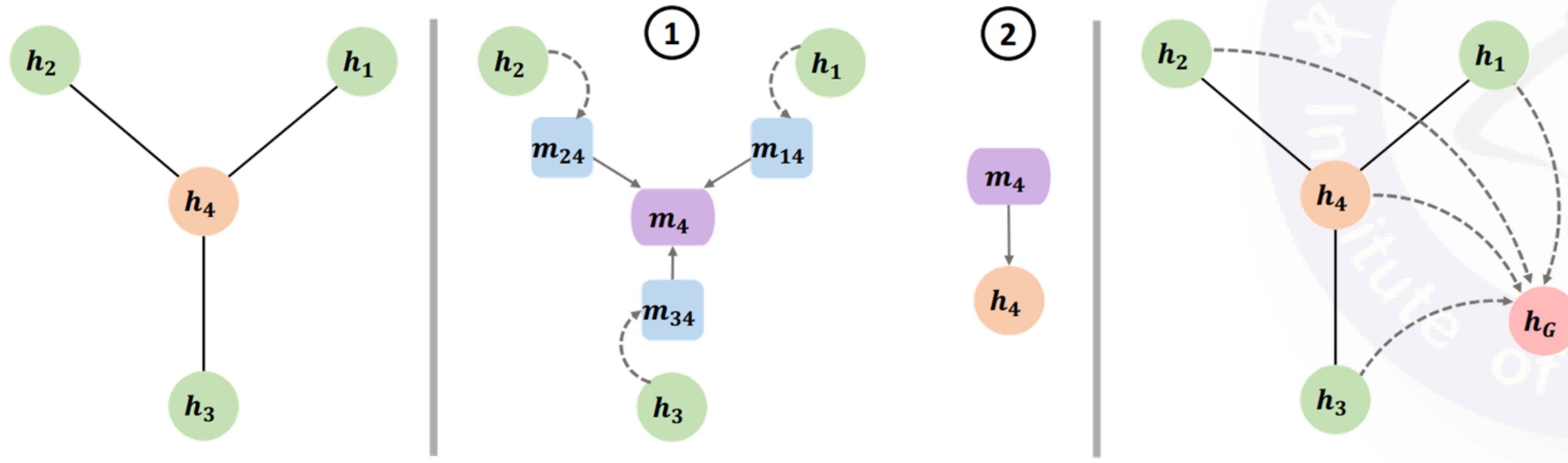
# Message-Passing GNN

## (a) Initialization

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

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

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



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

arXiv:2209.05582

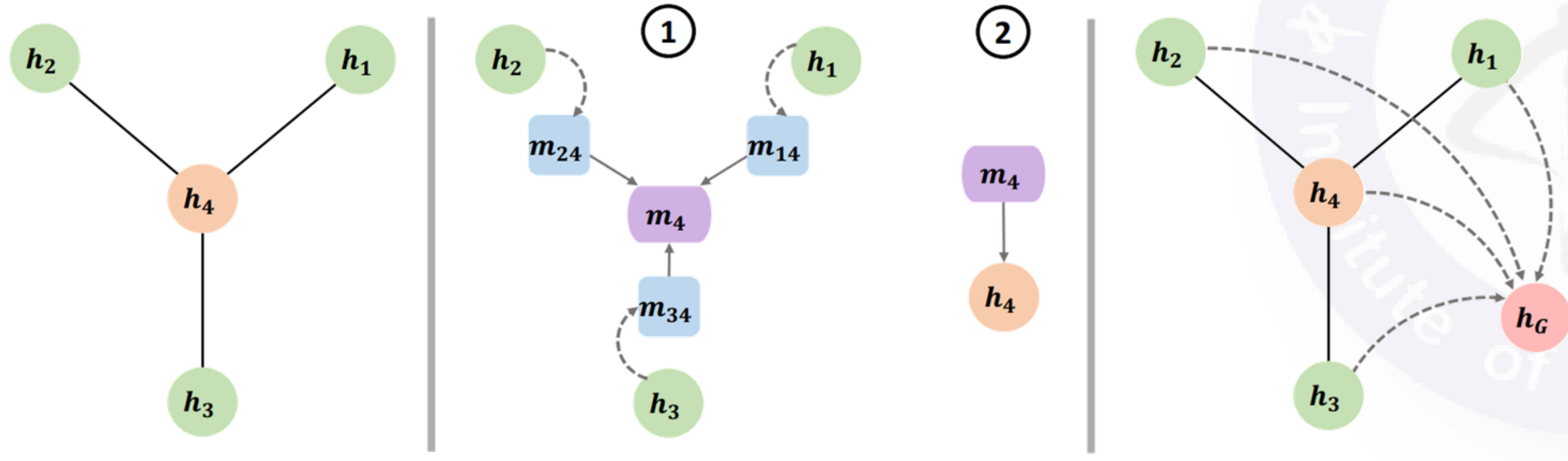
# Message-Passing GNN

## (b) Message-passing function

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

② Update (transformer): $$\mathbf{h}_i^{(k)} = \phi_u^{(k)} = \left(\mathbf{h}_i^{(k-1)}, \mathbf{m}_i^{(k)}\right)$$

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



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

arXiv:2209.05582

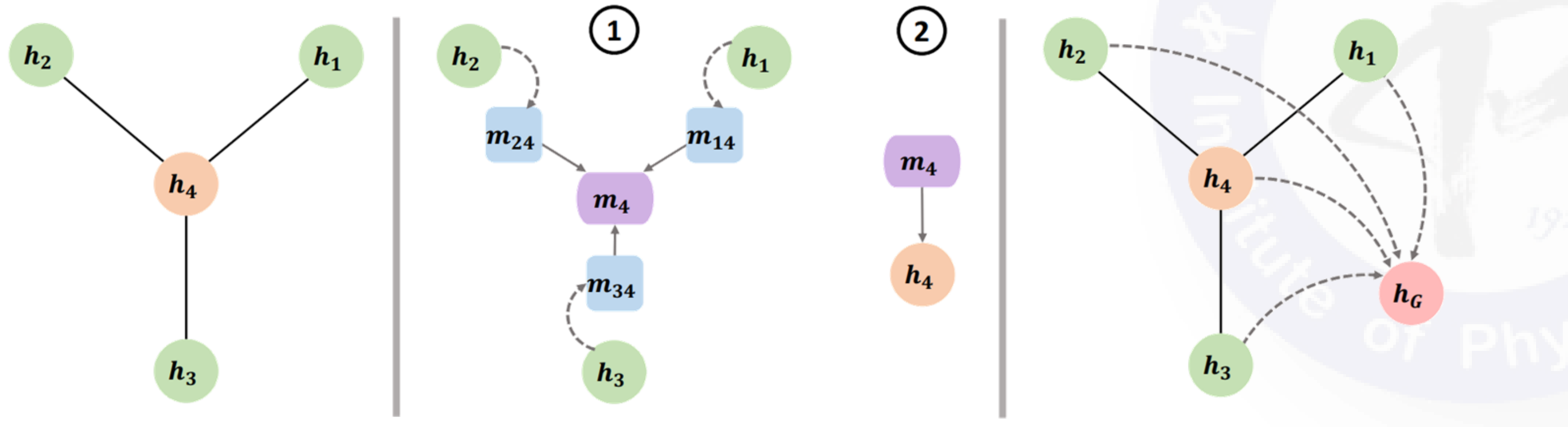
## Message-Passing GNN

### (c) Readout operations

After the last message-passing layer:

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

$R(\cdot)$: readout function.



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

arXiv:2209.05582

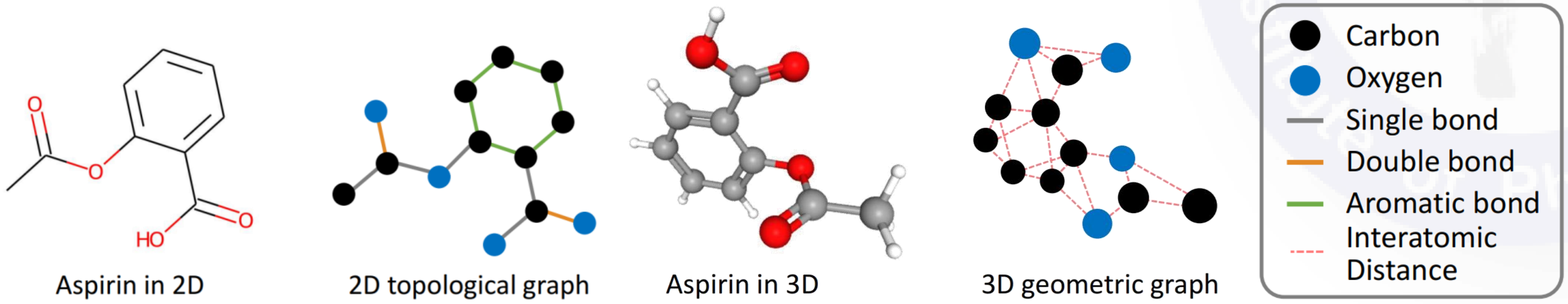
# Molecular GNN

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.

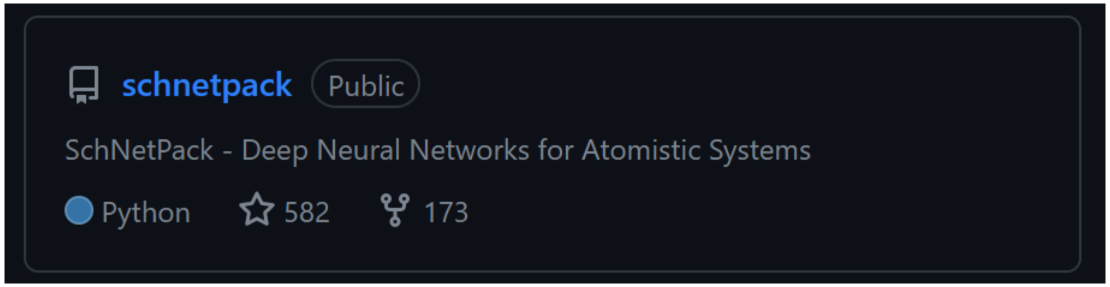


arXiv:2209.05582

# Molecular GNN

GNNs for molecules in 3D Euclidean space:

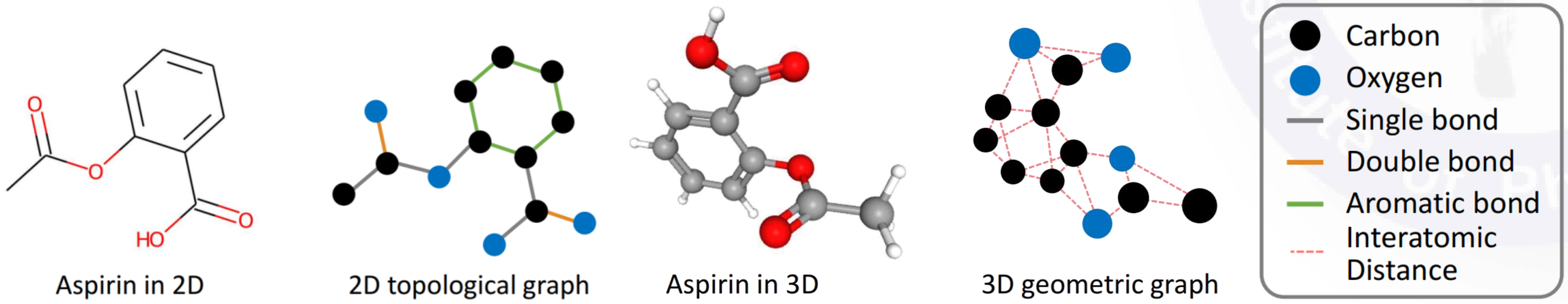
- Deep tensor neural network (DTNN): model distance in message-passing.
- **SchNet**: well designed layers to model local correlations, effectively encodes 3D distance to GNN, and inspires many follow-up works.



schnetpack Public

SchNetPack - Deep Neural Networks for Atomistic Systems

Python ☆ 582 173



arXiv:2209.05582

# 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.

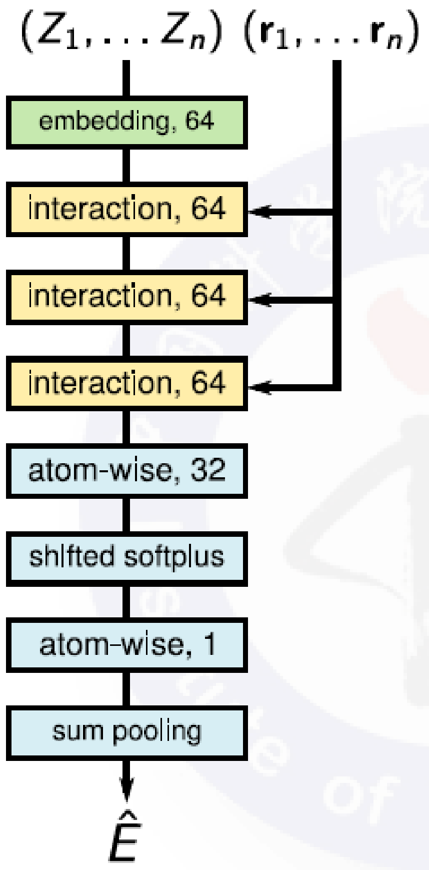
Speed up the exploration of chemical space.

Consider fundamental symmetries of atomistic systems.

rotational and translational invariance as well as invariance to atom indexing

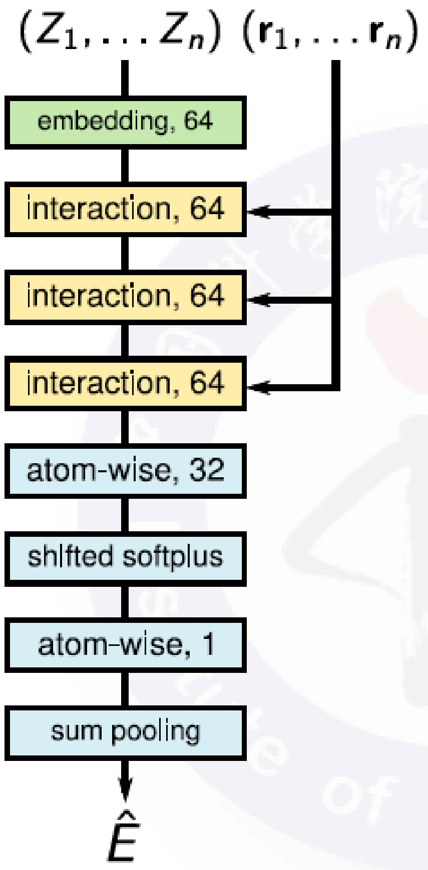
# Method

- 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.



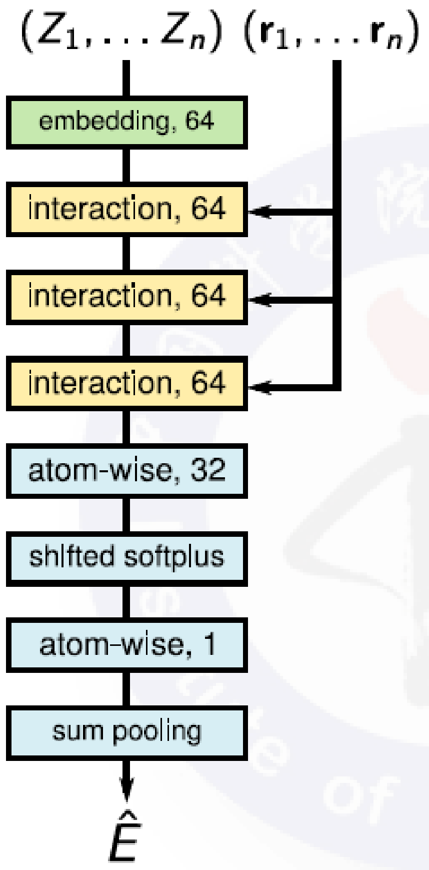
# Method

- 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 atom-wise updates of the feature representation and pooling of the resulting atom-wise energy.



# Molecular representation

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

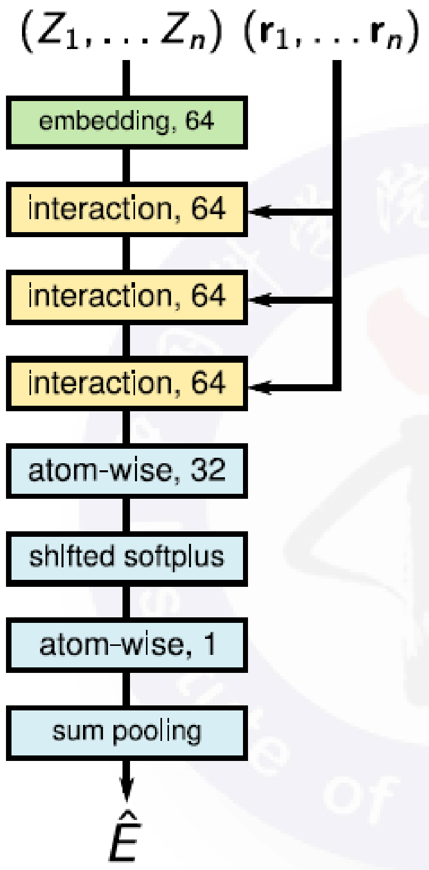


# Atom-wise layers

- Are dense layers.
- Applied separately to the representations $\mathbf{x}_i^l$ of each atom $i$:

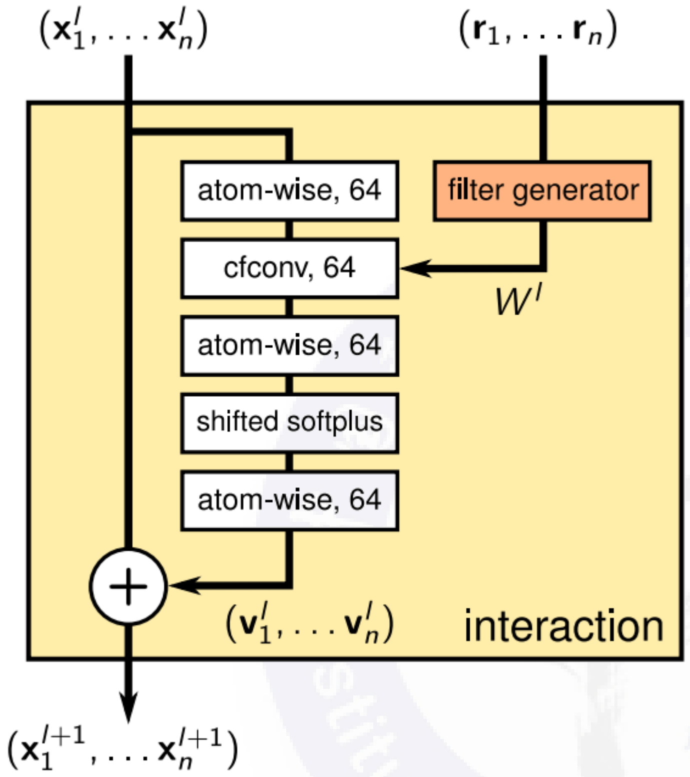
$$\mathbf{x}_i^{l+1} = W^l \mathbf{x}_i^l + \mathbf{b}^l$$

  - Weights $W^l$ and biases $b^l$ 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 $W^l$ that maps the atom positions to the corresponding values of the filter bank.



$(\mathbf{x}_1^l, \ldots \mathbf{x}_n^l)$
$(\mathbf{r}_1, \ldots \mathbf{r}_n)$
atom-wise, 64
filter generator
cfconv, 64
$W^l$
atom-wise, 64
shifted softplus
atom-wise, 64
$(\mathbf{v}_1^l, \ldots \mathbf{v}_n^l)$
interaction
$(\mathbf{x}_1^{l+1}, \ldots \mathbf{x}_n^{l+1})$

$$\mathbf{x}_i^{l+1} = (X^l * W^l)_i$$
$$= \mathbf{x}_j^l \circ W^l(\mathbf{r}_j - \mathbf{r}_i)$$

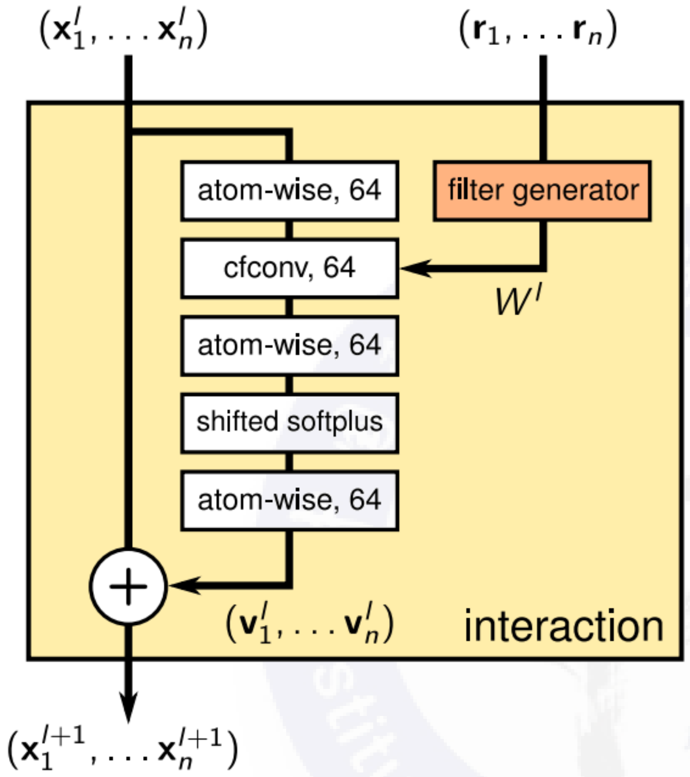
# Interaction blocks

- Activation functions: shifted softplus

  $$\mathrm{ssp}(x)=\ln(0.5\, e^{x}+0.5)$$

  - 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.


$(\mathbf{x}_1^l, \ldots \mathbf{x}_n^l)$
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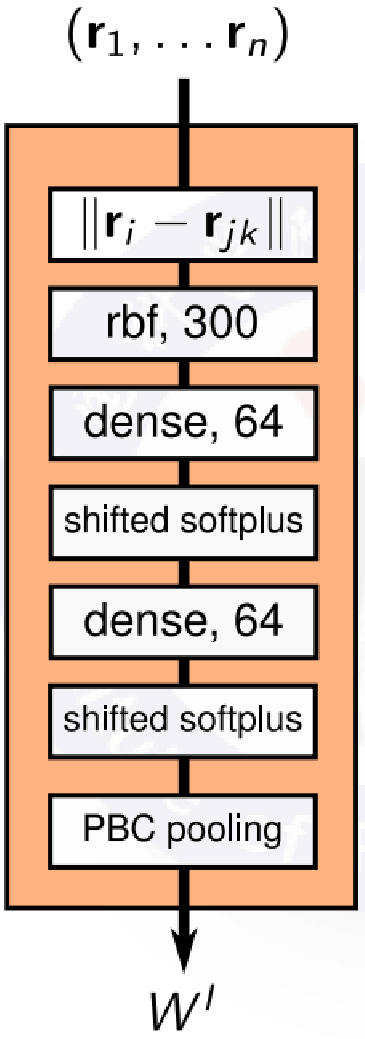
$(\mathbf{v}_1^l, \ldots \mathbf{v}_n^l)$
interaction
$(\mathbf{x}_1^{l+1}, \ldots \mathbf{x}_n^{l+1})$

# 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:

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



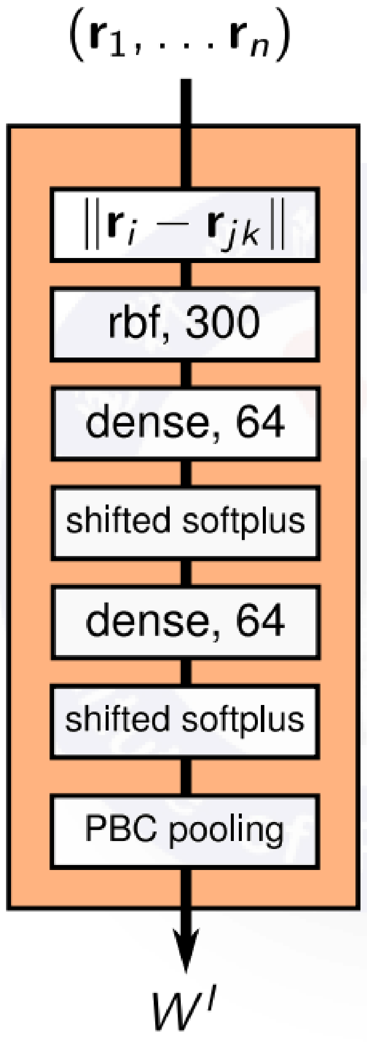
# Filter-generating networks

Rotationally invariant

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

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

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



# Filter-generating networks

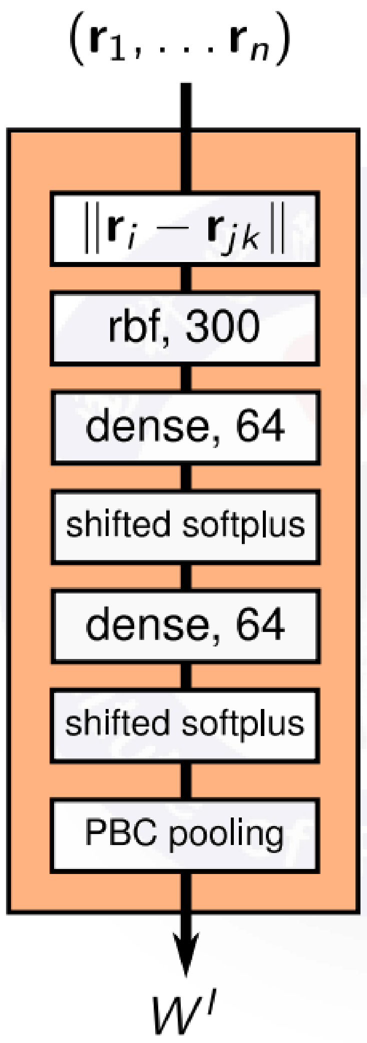
Periodic boundary conditions

- 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 $\|\mathbf{r}_{jb} - \mathbf{r}_{ia}\| < r_{\text{cut}}$.

$$\mathbf{x}_i^{l+1} = \mathbf{x}_{im}^{l+1} = \frac{1}{n_{\text{neighbors}}} \sum_{j,n} \mathbf{x}_{jn}^l \circ \tilde{W}^l(\mathbf{r}_{jn} - \mathbf{r}_{im})$$
$$= \frac{1}{n_{\text{neighbors}}} \sum_j \mathbf{x}_j^l \circ \underbrace{\left( \sum_n \tilde{W}^l(\mathbf{r}_{jn} - \mathbf{r}_{im}) \right)}_{W}$$

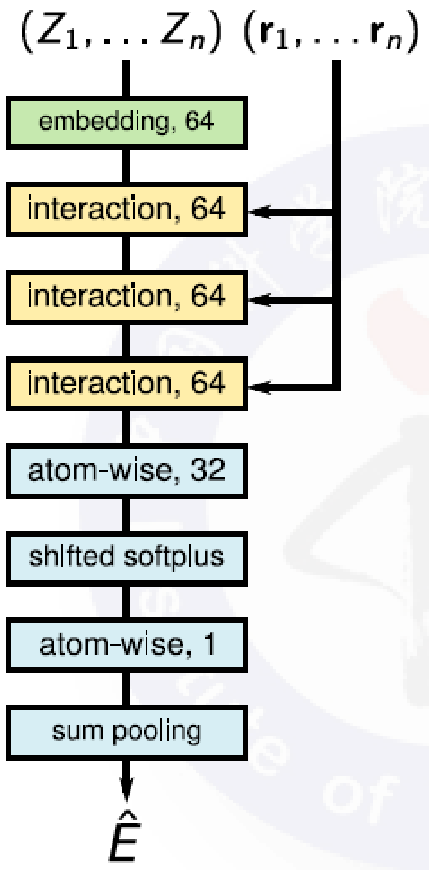
- More stable when normalizing the filter response $\mathbf{x}_i^{l+1}$ by the number of atoms within the cutoff range.



# Property prediction

- Compute atom-wise contributions $\hat{P}_i$ from the fully-connected prediction network.
- Calculate the final prediction $\hat{P}$ 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:

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



# 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:

$$\ell\left(\left(\hat{E}, \mathbf{F}_1, \ldots, \mathbf{F}_n\right), \left(E, \mathbf{F}_1, \ldots, \mathbf{F}_n\right)\right) = \rho \left\| E - \hat{E} \right\|^2 + \frac{1}{n_{\text{atoms}}} \sum_{i=0}^{n_{\text{atoms}}} \left\| \mathbf{F}_i - \left( -\frac{\partial \hat{E}}{\partial \mathbf{R}_i} \right) \right\|^2$$

  - *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**

$$\ddot{J}_{KL} = h\frac{\gamma_K}{2\pi}\frac{\gamma_L}{2\pi}\frac{d^2E}{d\mathbf{M}_K d\mathbf{M}_L}$$

**Scalar Coupling Constant**

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

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

**Quantum Mechanics**

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

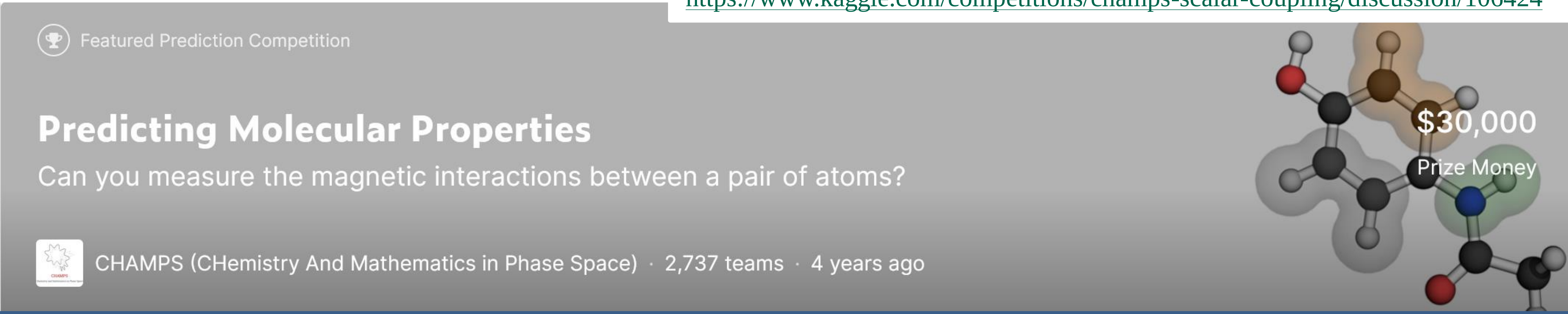
**DSO** **PSO** **FC+SD**

**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



Featured Prediction Competition

**Predicting Molecular Properties**

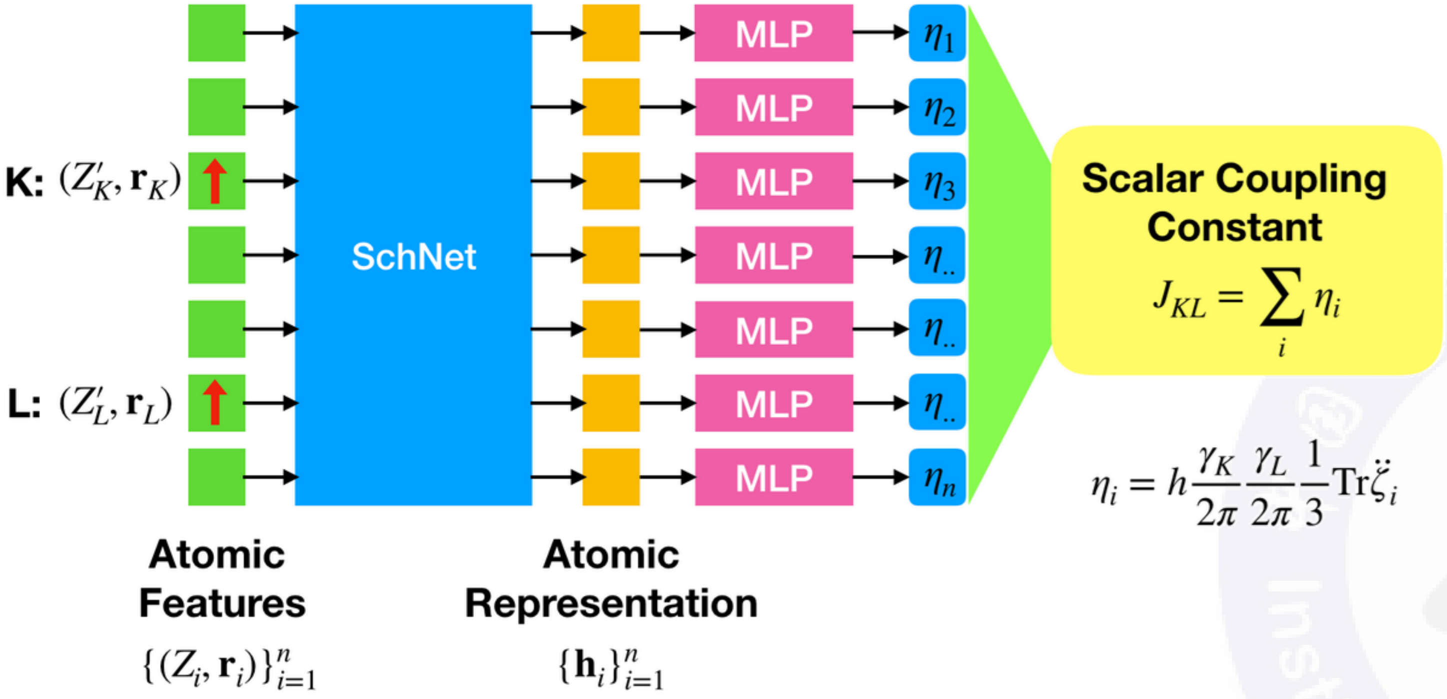
Can you measure the magnetic interactions between a pair of atoms?

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

$30,000

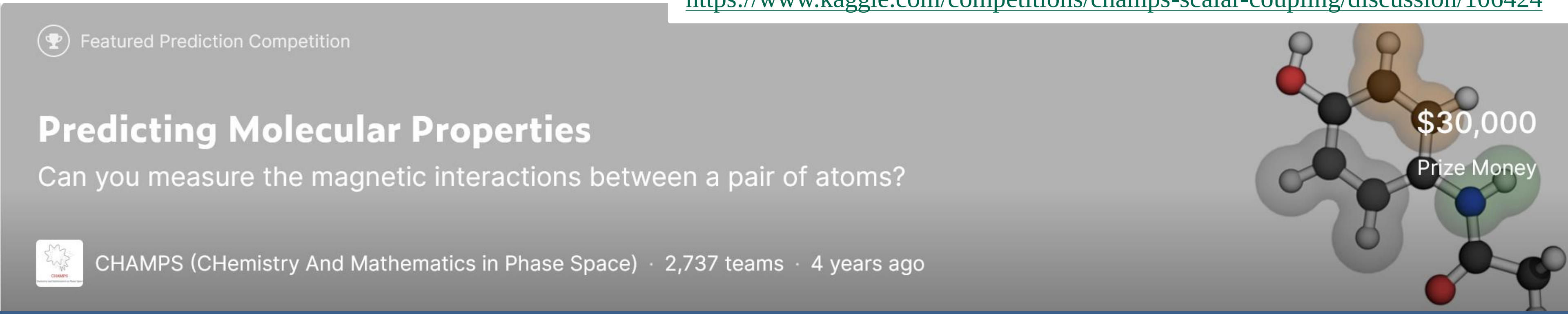
Prize Money

# Kaggle: predict scalar coupling constant



K: $(Z'_K, \mathbf{r}_K)$
L: $(Z'_L, \mathbf{r}_L)$
SchNet
MLP
$\eta_1$
$\eta_2$
$\eta_3$
$\eta_{..}$
$\eta_n$
Scalar Coupling Constant
$J_{KL} = \sum_i \eta_i$
$\eta_i = h \frac{\gamma_K}{2\pi} \frac{\gamma_L}{2\pi} \frac{1}{3} \mathrm{Tr} \ddot{\zeta}_i$
Atomic Features
$\{(Z_i, \mathbf{r}_i)\}_{i=1}^n$
Atomic Representation
$\{\mathbf{h}_i\}_{i=1}^n$

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



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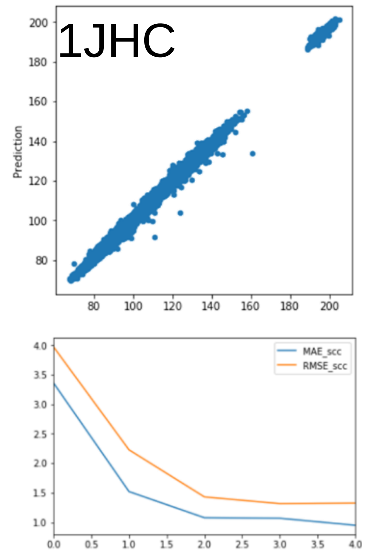
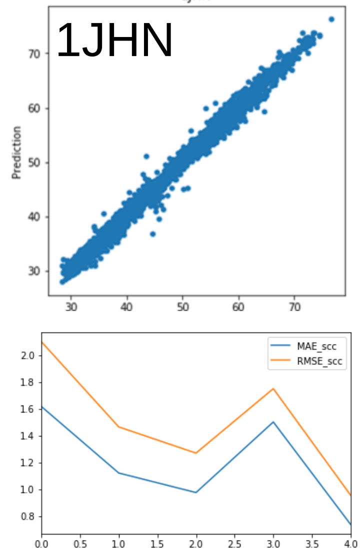
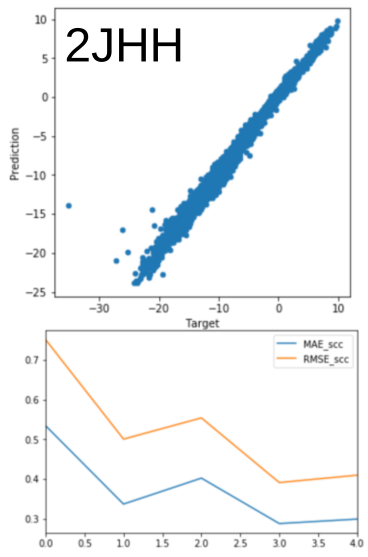
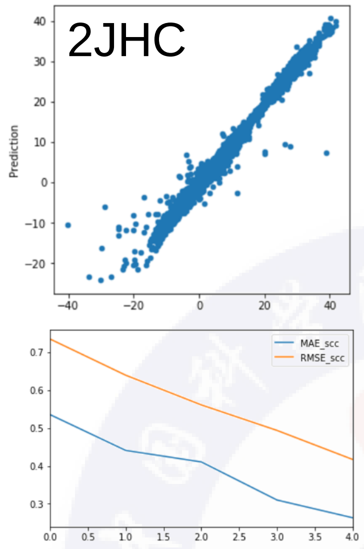
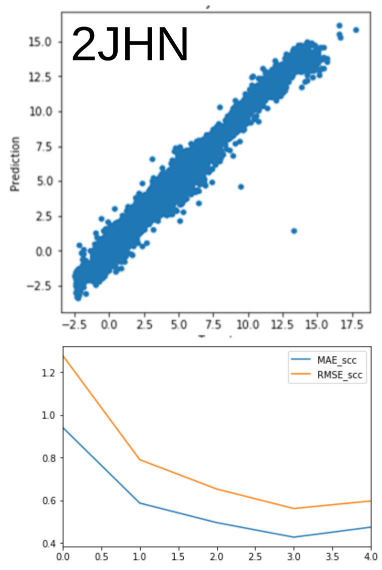
# Result

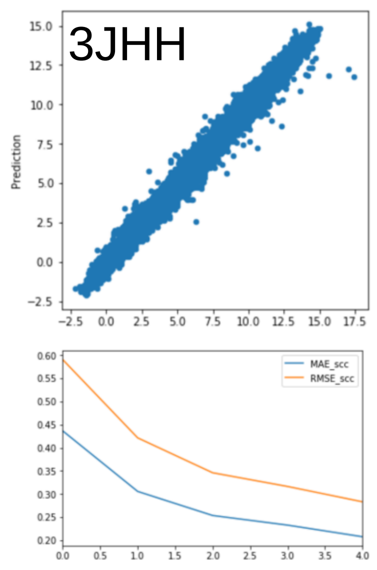

1JHC
Prediction
MAE_scc
RMSE_scc

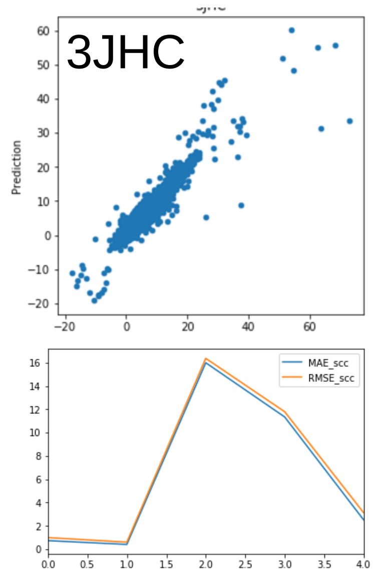

1JHN
Prediction
MAE_scc
RMSE_scc


2JHH
Prediction
Target
MAE_scc
RMSE_scc


2JHC
Prediction
MAE_scc
RMSE_scc


2JHN
Prediction
MAE_scc
RMSE_scc


3JHH
Prediction
MAE_scc
RMSE_scc


3JHC
Prediction
MAE_scc
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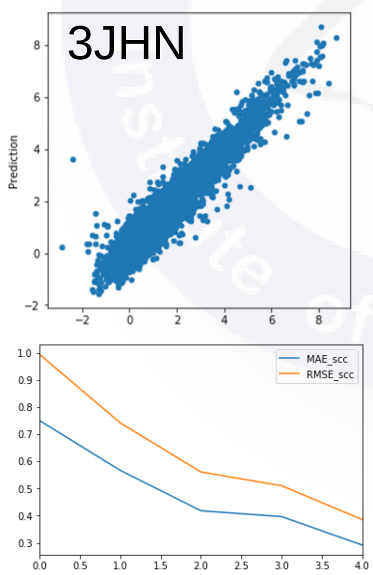
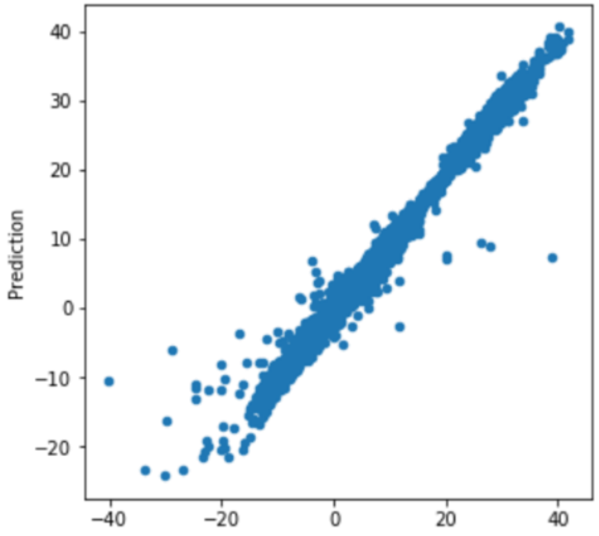
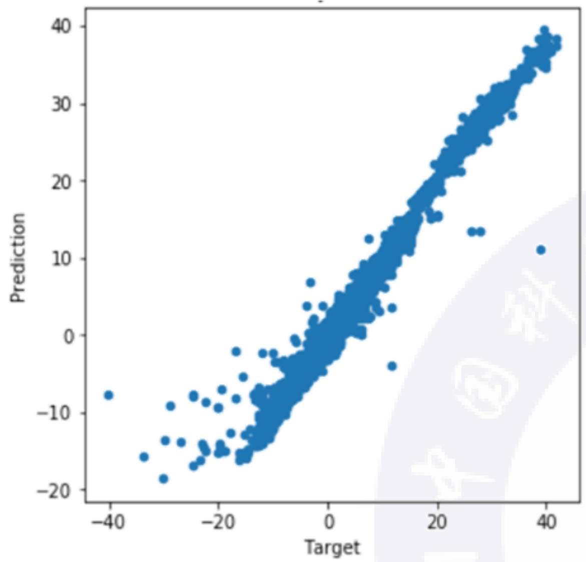
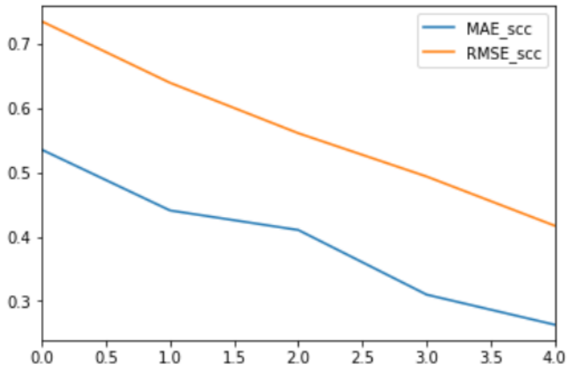

3JHN
Prediction
MAE_scc
RMSE_scc

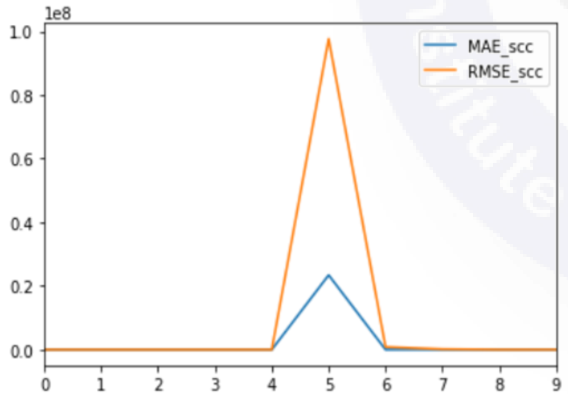
# Test: increase epoch steps to 10



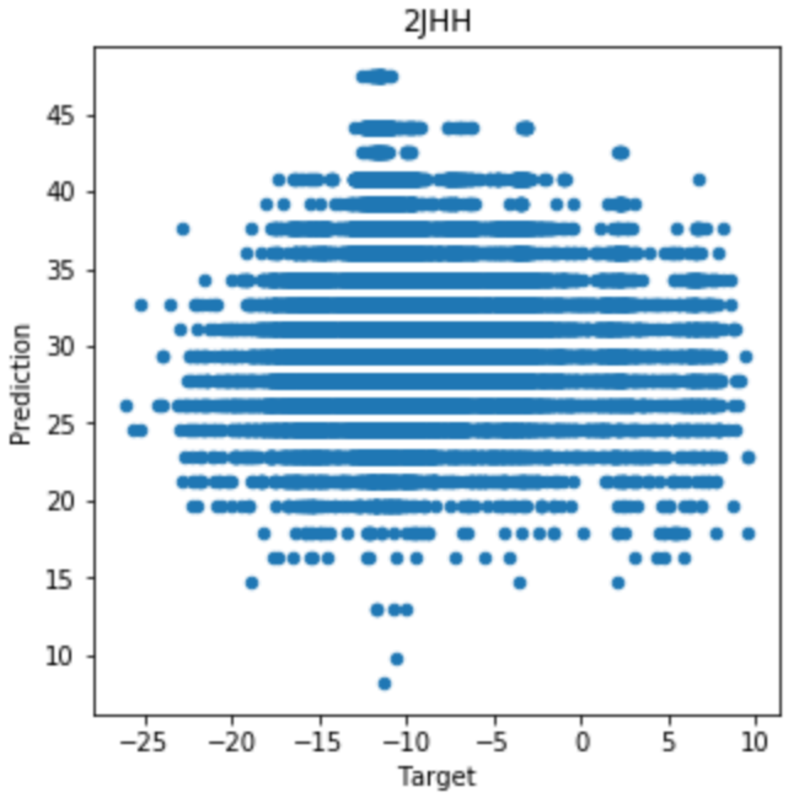


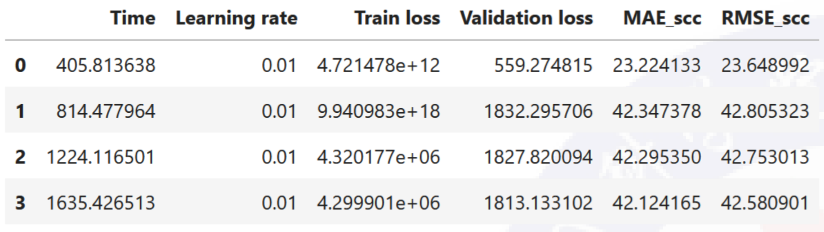
2JHC





# 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 |

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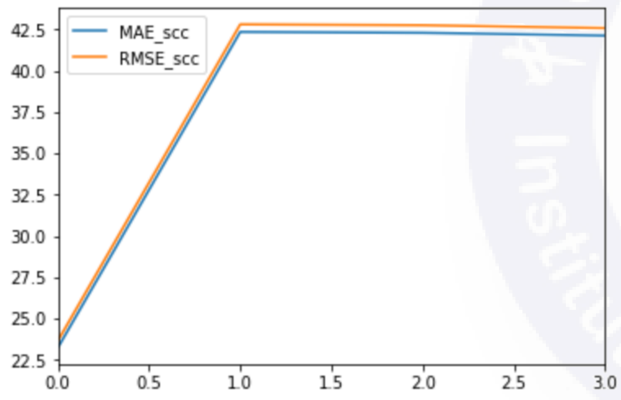
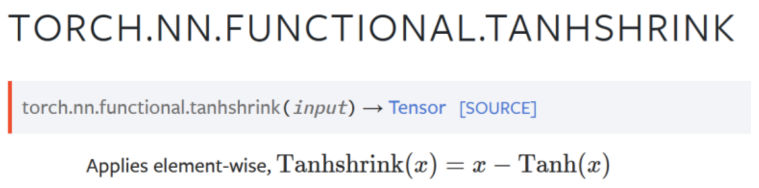


# Test: change activation function

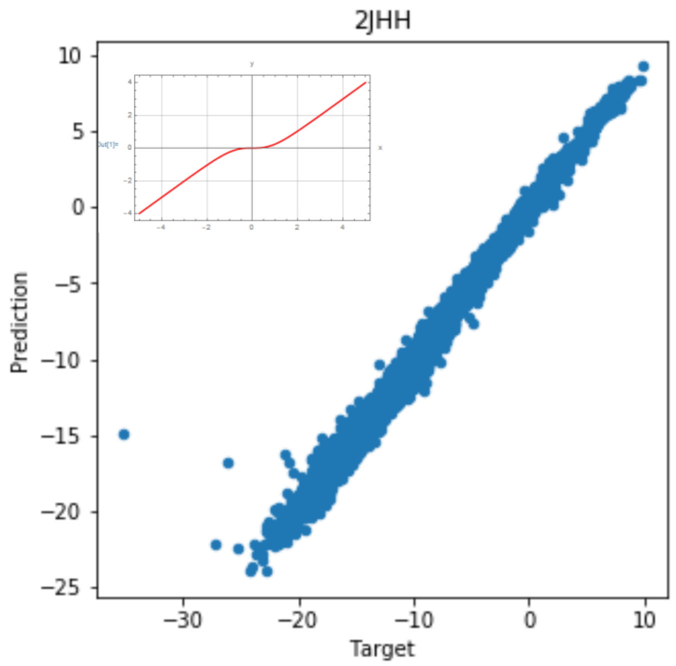


TORCH.NN.FUNCTIONAL.TANHSHRINK

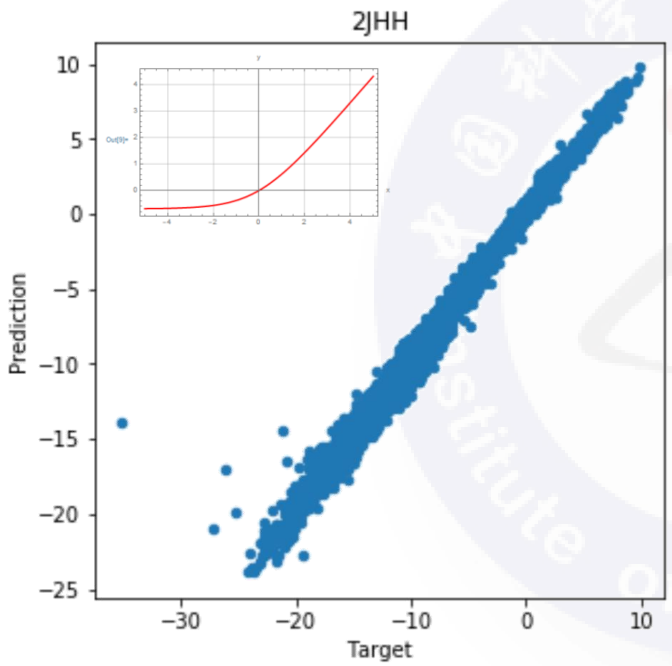
`torch.nn.functional.tanhshrink(input) → Tensor [SOURCE]`

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

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



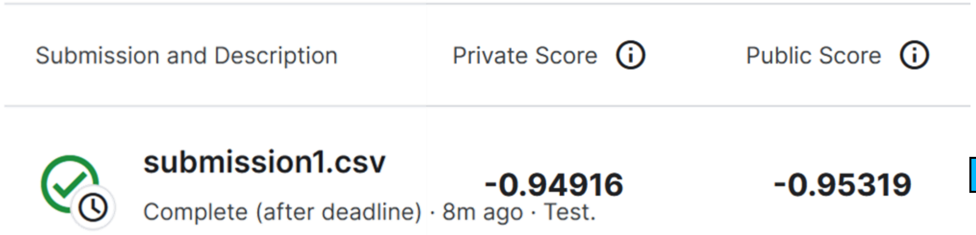
|  | RMSE | MAE | log(MAE) |
|---|---|---|---|
| 0 | 0.346743 | 0.233726 | -1.453607 |



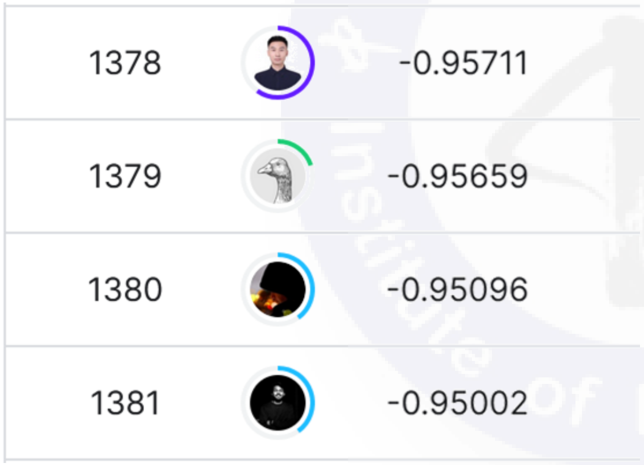
|  | RMSE | MAE | log(MAE) |
|---|---|---|---|
| **0** | 0.406484 | 0.287703 | -1.245828 |

## Score & Rank

1380th



| Submission and Description | Private Score | Public Score |
|---|---|---|
| submission1.csv<br>Complete (after deadline) · 8m ago · Test. | -0.94916 | -0.95319 |



| | |
|---|---|
| 1378 | -0.95711 |
| 1379 | -0.95659 |
| 1380 | -0.95096 |
| 1381 | -0.95002 |

Repo: https://github.com/InterStellarAlice/MolProPred

## THANKS!