中国科学院自动化研究所
模式识别实验室
New Laboratory of Pattern Recognition

中国科学院自动化研究所
Institute of Automation
Chinese Academy of Sciences

達摩院
DAMO ACADEMY

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# MolSpectra: Pre-training 3D Molecular Representation with Multi-modal Energy Spectra

Liang Wang[1,2], Shaozhen Liu[1], Yu Rong[3], Deli Zhao[3], Qiang Liu[1,2], Shu Wu[1,2], Liang Wang[1,2]

[1]Institute of Automation, Chinese Academy of Sciences
[2]University of Chinese Academy of Sciences
[3]DAMO Academy, Alibaba Group

ICLR

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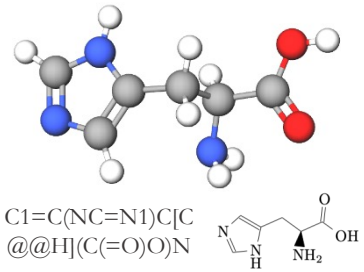
# Research Background

Molecular Generation, Molecular Optimization,
Molecular Spectroscopy Analysis

**Molecular Structure**




$f: u \rightarrow \mathbb{R}^d$

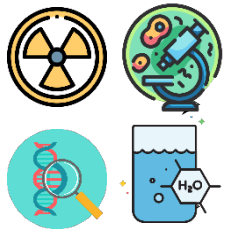
**Molecular Representation**

vector

$\mathbb{R}^d$

Feature representation, embedding

**Molecular Properties**




Solubility
Toxicity
Blood-Brain Barrier Permeability
Biological Activity
.....

**Application Fields**

- Drug discovery
- Materials science
- Biotechnology

Chemical Reaction, Retrosynthesis Planning,
Intermolecular Interactions, Target-Ligand Interaction

## Molecular Representation Learning

**Translate the molecular structures into vectorized molecular representations to understand and predict various molecular properties, interactions, chemical reactions.**

$$h = f(molecule)$$

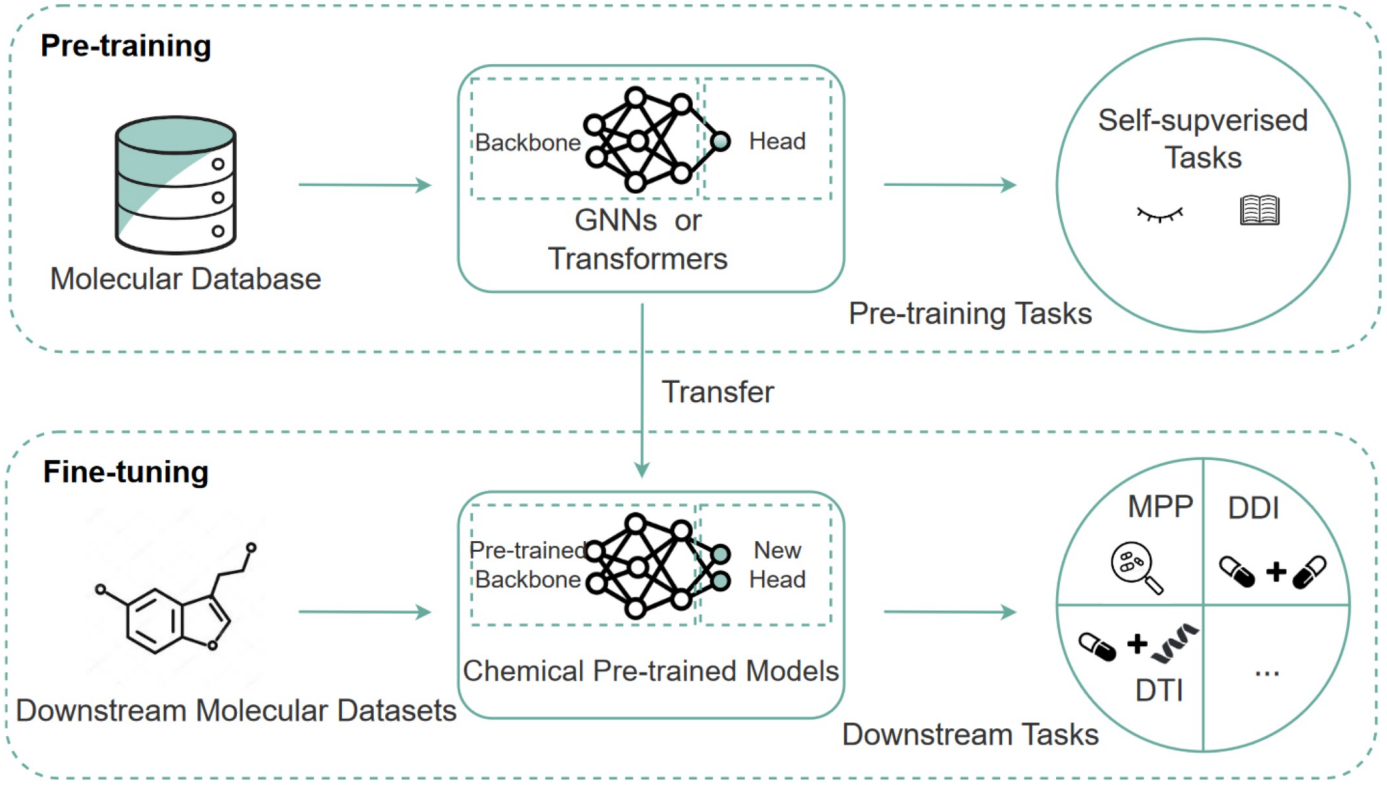
# Research Background

**Challenges of supervised molecular representation learning**

**(1) Scarcity of labeled data.**

**(2) Poor out-of-distribution generalization capability.**

**Pipeline of Molecular Representation Pre-training**




- ✓ Pre-trained on large-scale unlabeled molecules.
- ✓ Fine-tuned on various downstream tasks.

# Research Background

- **Denoising as learning a force field.**
  - It is not feasible to learn molecular force field directly, since it is either unknown or expensive to evaluate.
  - Alternative: approximate the data-generating force field with one that can be cheaply evaluated.
  - Prove that the denoising objective is equivalent to learning the molecular force field:
    - Molecular structure: $\mathbf{x} \in \mathbb{R}^{3N}$
    - The structure follows the Boltzmann distribution: $p_{\text{physical}}(\mathbf{x}) \propto \exp(-E(\mathbf{x}))$
    - Force field: $\nabla_{\mathbf{x}} \log p_{\text{physical}}(\mathbf{x}) = -\nabla_{\mathbf{x}} E(\mathbf{x})$
    - Approximate $p_{\text{physical}}$ with a mixture of Gaussians centered at the known equilibrium structures

$$p_{\text{physical}}(\tilde{\mathbf{x}}) \approx q_\sigma(\tilde{\mathbf{x}}) \coloneqq \frac{1}{n}\sum_{i=1}^{n} q_\sigma(\tilde{\mathbf{x}} \mid \mathbf{x_i})$$

where $q_\sigma(\tilde{\mathbf{x}} \mid \mathbf{x_i}) = \mathcal{N}(\tilde{\mathbf{x}}; \mathbf{x_i}, \sigma^2 I_{3N})$.

[1] Sheheryar Zaidi, Michael Schaarschmidt, James Martens, Hyunjik Kim, Yee Whye Teh, Alvaro Sanchez-Gonzalez, Peter Battaglia, Razvan Pascanu, Jonathan Godwin. **"Pre-Training via Denoising for Molecular Property Prediction."** In *ICLR*, 2023

# Research Background

- **Denoising as learning a force field. (Cont.)**
  - Learning the force field now yields a score-matching objective:

$$\mathbb{E}_{q_\sigma(\tilde{\mathbf{x}})}[\| \mathrm{GNN}_\theta(\tilde{\mathbf{x}}) - \nabla_{\tilde{\mathbf{x}}} \log q_\sigma(\tilde{\mathbf{x}}) \|^2]$$

  - According to reference [1], minimizing the following two objectives is equivalent:

$$J_1(\theta) = \mathbb{E}_{q_\sigma(\tilde{\mathbf{x}})}[\| \mathrm{GNN}_\theta(\tilde{\mathbf{x}}) - \nabla_{\tilde{\mathbf{x}}} \log q_\sigma(\tilde{\mathbf{x}}) \|^2]$$

$$J_2(\theta) = \mathbb{E}_{q_\sigma(\tilde{\mathbf{x}},\mathbf{x})}[\| \mathrm{GNN}_\theta(\tilde{\mathbf{x}}) - \nabla_{\tilde{\mathbf{x}}} \log q_\sigma(\tilde{\mathbf{x}} \mid \mathbf{x}) \|^2]$$

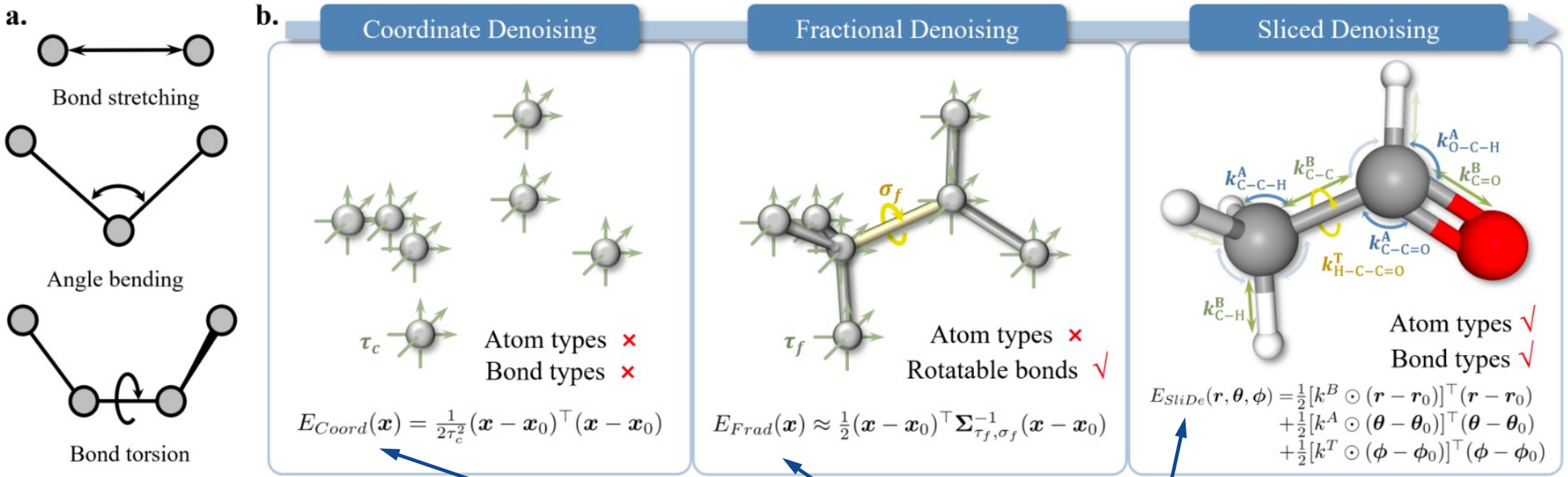
  - Thus, the objective in Eq. (1) is equivalent to:

$$\mathbb{E}_{q_\sigma(\tilde{\mathbf{x}},\mathbf{x})}[\| \mathrm{GNN}_\theta(\tilde{\mathbf{x}}) - \nabla_{\tilde{\mathbf{x}}} \log q_\sigma(\tilde{\mathbf{x}} \mid \mathbf{x}) \|^2] = \mathbb{E}_{q_\sigma(\tilde{\mathbf{x}},\mathbf{x})}\left[\| \mathrm{GNN}_\theta(\tilde{\mathbf{x}}) - \frac{\mathbf{x}-\tilde{\mathbf{x}}}{\sigma^2} \|^2\right]$$

***Establishing the relationship between 3D geometries and the energy states of molecular systems is an effective pathway to learn 3D molecular representations.***

[1] Pascal Vincent. **"A Connection Between Score Matching and Denoising Autoencoders."** *Neural Computation* July 2011

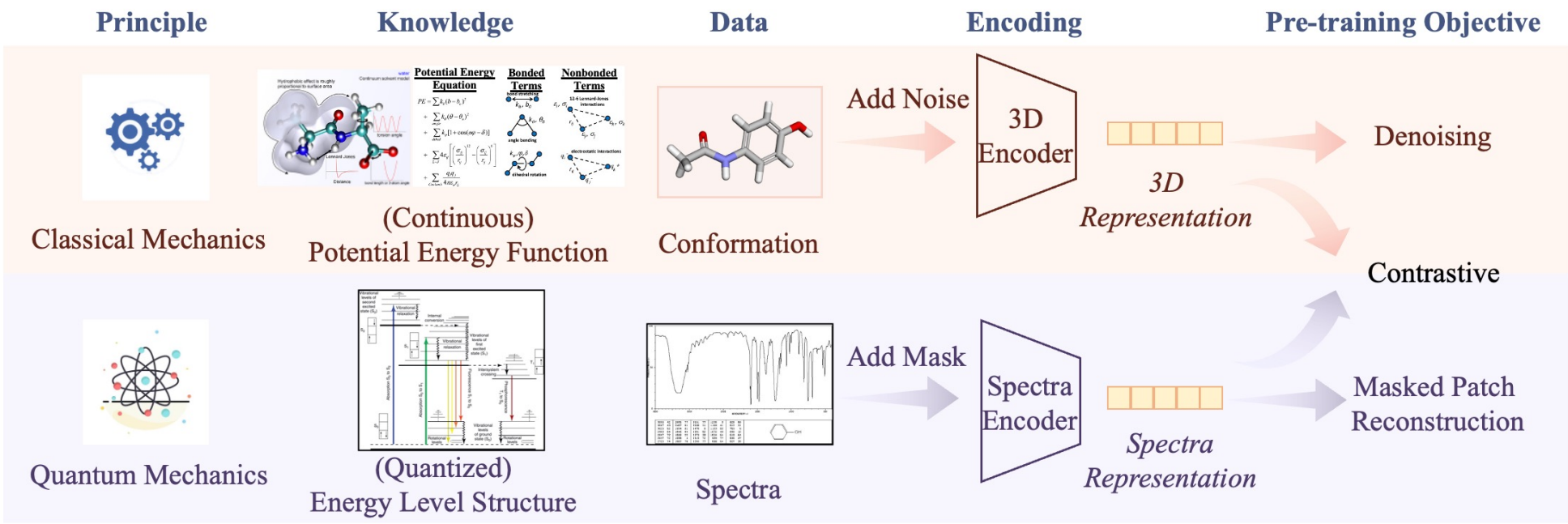
# Research Background

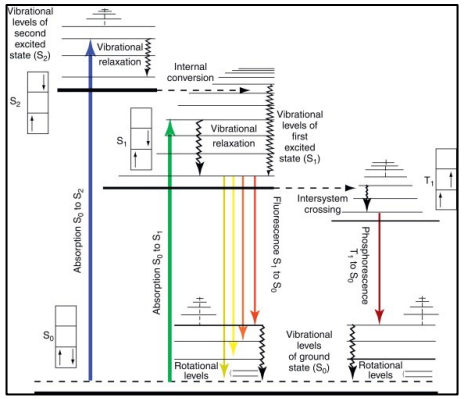


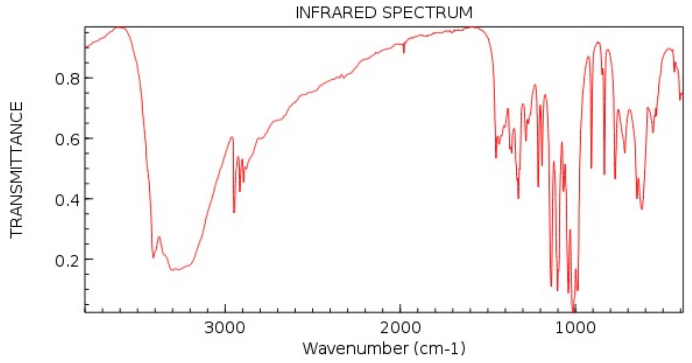

$$\mathcal{L}_{\text{Denoising}}(\mathcal{M}) = \mathbb{E}_{p(\boldsymbol{x}|\boldsymbol{x}_0)p(\boldsymbol{x}_0)}\|\text{GNN}_\theta(\boldsymbol{x}) - (\boldsymbol{x}-\boldsymbol{x}_0)\|^2$$
$$\simeq \mathbb{E}_{p(\boldsymbol{x})}\|\text{GNN}_\theta(\boldsymbol{x}) - (-\nabla_{\boldsymbol{x}} E(\boldsymbol{x}))\|^2,$$

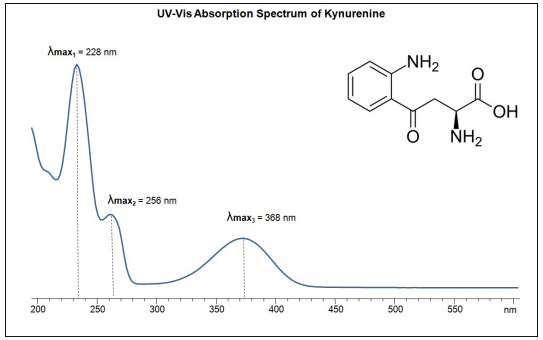
[1] Yuyan Ni, Shikun Feng, Wei-Ying Ma, Zhi-Ming Ma, Yanyan Lan. **"Sliced Denoising: A Physics-Informed Molecular Pre-Training Method."** In *ICLR*, 2024

# Motivation

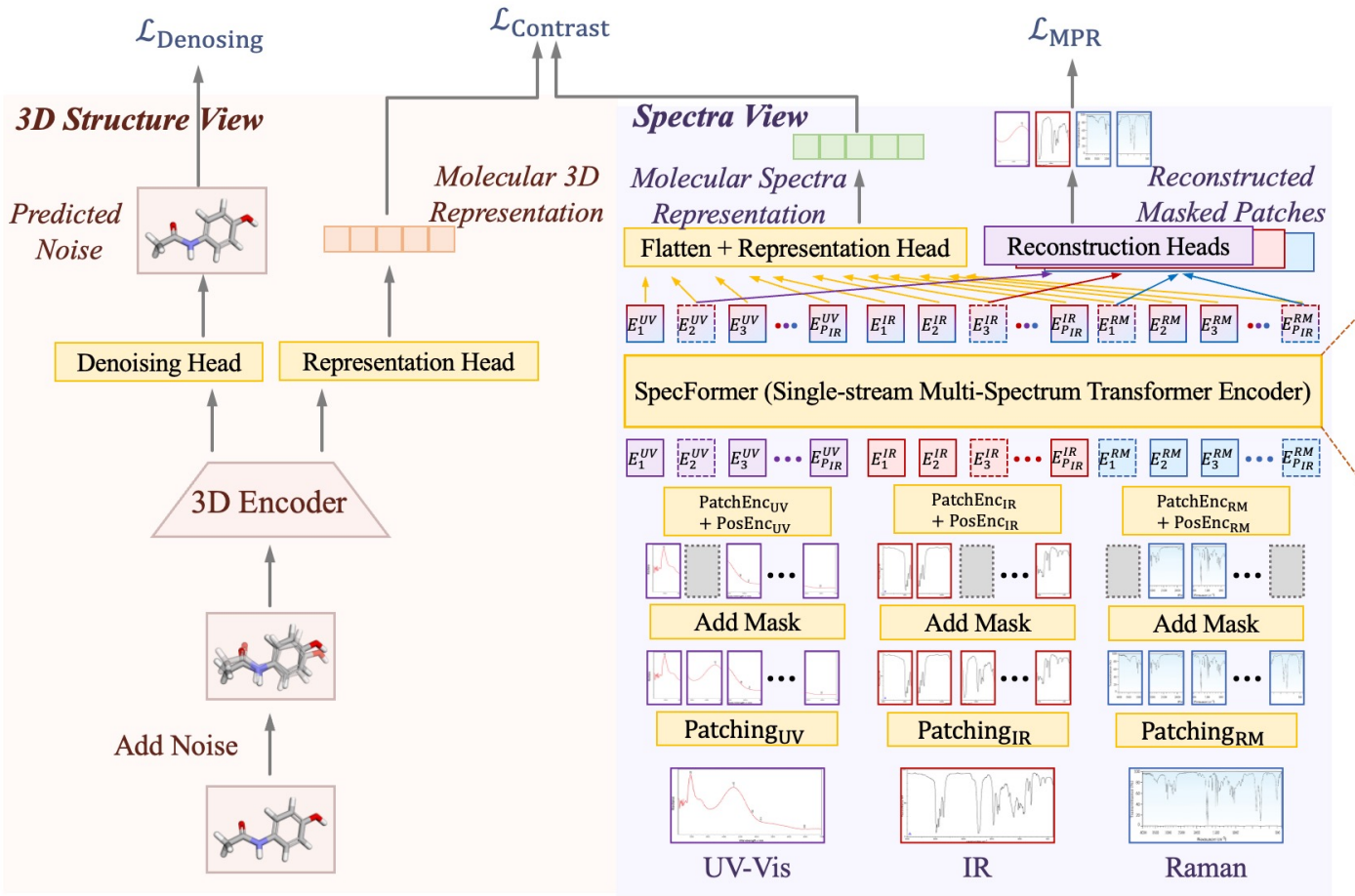

Principle
Knowledge
Data
Encoding
Pre-training Objective
Potential Energy Equation
Bonded Terms
Nonbonded Terms
Add Noise
3D Encoder
3D Representation
Denoising
Classical Mechanics
(Continuous) Potential Energy Function
Conformation
Contrastive
Quantum Mechanics
(Quantized) Energy Level Structure
Spectra
Add Mask
Spectra Encoder
Spectra Representation
Masked Patch Reconstruction

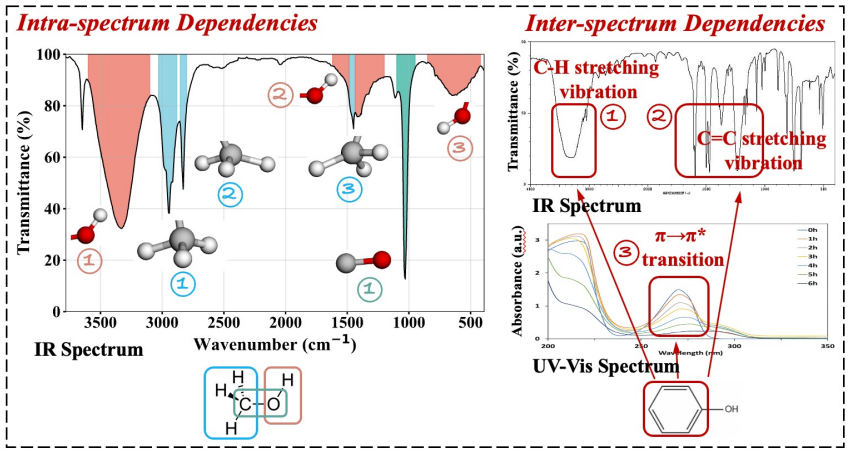

Vibrational levels of second excited state ($S_2$)
Vibrational relaxation
Internal conversion
Vibrational levels of first excited state ($S_1$)
Intersystem crossing
Absorption $S_0$ to $S_2$
Absorption $S_0$ to $S_1$
Fluorescence $S_1$ to $S_0$
Phosphorescence $T_1$ to $S_0$
Vibrational levels of ground state ($S_0$)
Rotational levels


INFRARED SPECTRUM
TRANSMITTANCE
0.8
0.6
0.4
0.2
3000
2000
1000
Wavenumber (cm-1)


UV-Vis Absorption Spectrum of Kynurenine
λmax1 = 228 nm
λmax2 = 256 nm
λmax3 = 368 nm
NH2
O
OH
O
NH2
200
250
300
350
400
450
500
550
nm

# MolSpectra




$$\mathcal{L} = \beta_{\text{Denoising}}\mathcal{L}_{\text{Denoising}} + \beta_{\text{MPR}}\mathcal{L}_{\text{MPR}} + \beta_{\text{Contrast}}\mathcal{L}_{\text{Contrast}}$$

# Experiments

## Effectiveness of Molecular Spectra in Training from Scratch

Table 1: Performance (MAE ↓) when training from scratch on QM9 dataset.

| Task<br>Units | $\mu$<br>(D) | $\alpha$<br>($a_0^3$) | homo<br>(meV) | lumo<br>(meV) | gap<br>(meV) | $R^2$<br>($a_0^2$) | ZPVE<br>(meV) | $U_0$<br>(meV) | $U$<br>(meV) | $H$<br>(meV) | $G$<br>(meV) | $C_v$<br>($\frac{cal}{mol \cdot K}$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| w/o spectra | 0.029 | 0.071 | 29 | 25 | 48 | 0.106 | 1.55 | 11 | 12 | 12 | 12 | 0.031 |
| w/ spectra | **0.027** | **0.049** | **28** | **24** | **43** | **0.084** | **1.45** | **10** | **11** | **10** | **10** | **0.030** |

# Experiments

## Effectiveness of Molecular Spectra in Representation Pre-Training

Table 2: Performance (MAE↓) on QM9 dataset. The compared methods are divided into two groups training from scratch and pre-training then fine-tuning. The best results are highlighted in bold.

| | $\mu$ (D) | $\alpha$ ($a_0^3$) | homo (meV) | lumo (meV) | gap (meV) | $R^2$ ($a_0^2$) | ZPVE (meV) | $U_0$ (meV) | $U$ (meV) | $H$ (meV) | $G$ (meV) | $C_v$ ($\frac{cal}{mol \cdot K}$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SchNet | 0.033 | 0.235 | 41.0 | 34.0 | 63.0 | 0.070 | 1.70 | 14.00 | 19.00 | 14.00 | 14.00 | 0.033 |
| EGNN | 0.029 | 0.071 | 29.0 | 25.0 | 48.0 | 0.106 | 1.55 | 11.00 | 12.00 | 12.00 | 12.00 | 0.031 |
| DimeNet++ | 0.030 | 0.044 | 24.6 | 19.5 | 32.6 | 0.330 | 1.21 | 6.32 | 6.28 | 6.53 | 7.56 | 0.023 |
| PaiNN | 0.012 | 0.045 | 27.6 | 20.4 | 45.7 | 0.070 | 1.28 | 5.85 | 5.83 | 5.98 | 7.35 | 0.024 |
| SphereNet | 0.025 | 0.045 | 22.8 | 18.9 | 31.1 | 0.270 | **1.12** | 6.26 | 6.36 | 6.33 | 7.78 | 0.022 |
| TorchMD-Net | 0.011 | 0.059 | 20.3 | 17.5 | 36.1 | **0.033** | 1.84 | 6.15 | 6.38 | 6.16 | 7.62 | 0.026 |
| Transformer-M | 0.037 | **0.041** | 17.5 | 16.2 | 27.4 | 0.075 | 1.18 | 9.37 | 9.41 | 9.39 | 9.63 | 0.022 |
| SE(3)-DDM | 0.015 | 0.046 | 23.5 | 19.5 | 40.2 | 0.122 | 1.31 | 6.92 | 6.99 | 7.09 | 7.65 | 0.024 |
| 3D-EMGP | 0.020 | 0.057 | 21.3 | 18.2 | 37.1 | 0.092 | 1.38 | 8.60 | 8.60 | 8.70 | 9.30 | 0.026 |
| Coord | 0.016 | 0.052 | 17.7 | 14.7 | 31.8 | 0.450 | 1.71 | 6.57 | 6.11 | 6.45 | 6.91 | **0.020** |
| MolSpectra | **0.011** | 0.048 | **15.5** | **13.1** | **26.8** | 0.410 | 1.71 | **5.67** | **5.45** | **5.87** | **6.18** | 0.021 |

# Experiments

## Effectiveness of Molecular Spectra in Representation Pre-Training

Table 3: Performance (MAE↓) on MD17 force prediction (kcal/mol/ Å). The methods are divided into two groups: training from scratch and pre-training then fine-tuning. The best results are in bold.

| | Aspirin | Benzene | Ethanol | Malonal -dehyde | Naphtha -lene | Salicy -lic Acid | Toluene | Uracil |
|---|---|---|---|---|---|---|---|---|
| SphereNet | 0.430 | 0.178 | 0.208 | 0.340 | 0.178 | 0.360 | 0.155 | 0.267 |
| SchNet | 1.350 | 0.310 | 0.390 | 0.660 | 0.580 | 0.850 | 0.570 | 0.560 |
| DimeNet | 0.499 | 0.187 | 0.230 | 0.383 | 0.215 | 0.374 | 0.216 | 0.301 |
| PaiNN | 0.338 | - | 0.224 | 0.319 | 0.077 | 0.195 | 0.094 | 0.139 |
| TorchMD-Net | 0.245 | 0.219 | 0.107 | 0.167 | 0.059 | 0.128 | 0.064 | 0.089 |
| SE(3)-DDM* | 0.453 | - | 0.166 | 0.288 | 0.129 | 0.266 | 0.122 | 0.183 |
| Coord | 0.211 | 0.169 | 0.096 | 0.139 | **0.053** | 0.109 | **0.058** | **0.074** |
| MolSpectra | **0.099** | **0.097** | **0.052** | **0.077** | 0.085 | **0.093** | 0.075 | 0.095 |

# Experiments

## Sensitivity Analysis of Patch Length, Stride, and Mask Ratio

Table 4: Sensitivity of patch length and stride.

| patch length | stride | overlap ratio | homo | lumo | gap |
|---|---|---|---|---|---|
| 20 | 5 | 75% | 15.9 | 13.7 | 28.0 |
| 20 | 10 | 50% | **15.5** | **13.1** | **26.8** |
| 20 | 15 | 25% | 16.1 | 13.6 | 28.1 |
| 20 | 20 | 0% | 15.7 | 13.5 | 27.5 |
| 16 | 8 | 50% | 16.0 | 13.4 | 27.6 |
| 30 | 15 | 50% | 15.9 | 14.0 | 28.1 |

Table 5: Sensitivity of mask ratio.

| mask ratio | homo | lumo | gap |
|---|---|---|---|
| 0.05 | 15.7 | 13.4 | 29.7 |
| 0.10 | **15.5** | **13.1** | **26.8** |
| 0.15 | 15.7 | 13.5 | 28.0 |
| 0.20 | 16.0 | 13.6 | 28.1 |
| 0.25 | 16.3 | 13.5 | 28.0 |
| 0.30 | 16.2 | 13.7 | 29.0 |

## Ablation Study of Spectral Modalities

Table 7: Ablation of spectral modalities.

| UV-Vis | IR | Raman | homo | lumo | gap |
|---|---|---|---|---|---|
| ✓ | ✓ | ✓ | 15.5 | 13.1 | 26.8 |
| - | ✓ | ✓ | 15.8 | 13.3 | 27.1 |
| ✓ | - | ✓ | 16.6 | 14.1 | 28.9 |
| ✓ | ✓ | - | 16.1 | 13.9 | 28.3 |

# Experiments

## Visualization of Attention Patterns and Learned Spectra Representations in SpecFormer

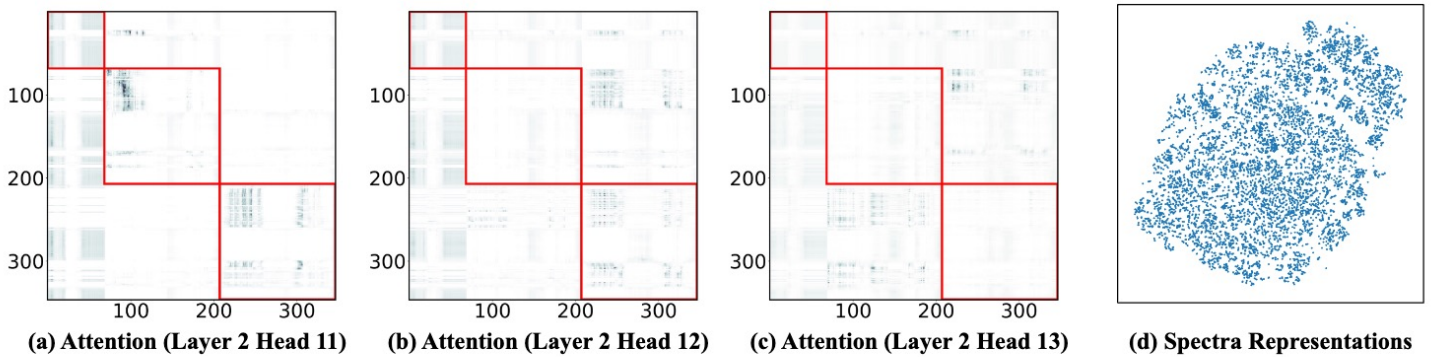



Figure A2: (a-c) Attention maps from three attention heads in SpecFormer. Different heads model distinct dependencies. (d) t-SNE visualization of the spectra representations produced by SpecFormer.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# Thank you for your attention!

Contact： liang.wang@cripac.ia.ac.cn