Molecular Pre-trained Models

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Outline

SMILES

MULTIMODAL MOLECULAR PRETRAINING VIA MODALITY BLENDING

SMILES

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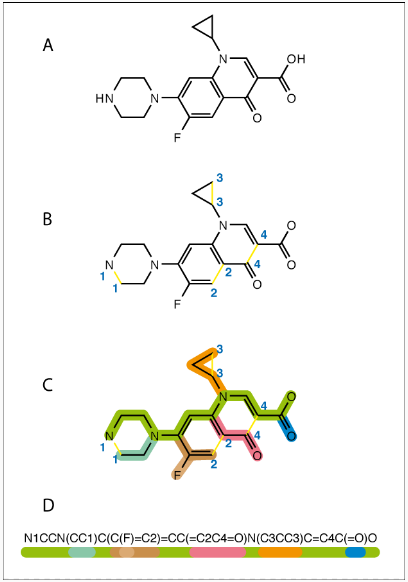
The **simplified molecular-input line-entry system (SMILES)** is a specification in the form of a line notation for describing the structure of chemical species using short ASCII strings.

- Atoms are represented by the standard abbreviation of the chemical elements, in square brackets, such as [Au] for gold.
    - Brackets may be omitted in the common case of atoms: B, C, N, O, P, S, F, Cl, Br, or I
- single bond Hydrogen atoms are often omitted. For instance, the SMILES for water is written as either O.
- Double bonds are represented by ”=”; The three keys are represented by ”♯”.Carbon dioxide containing double bonds is expressed as O=C=O

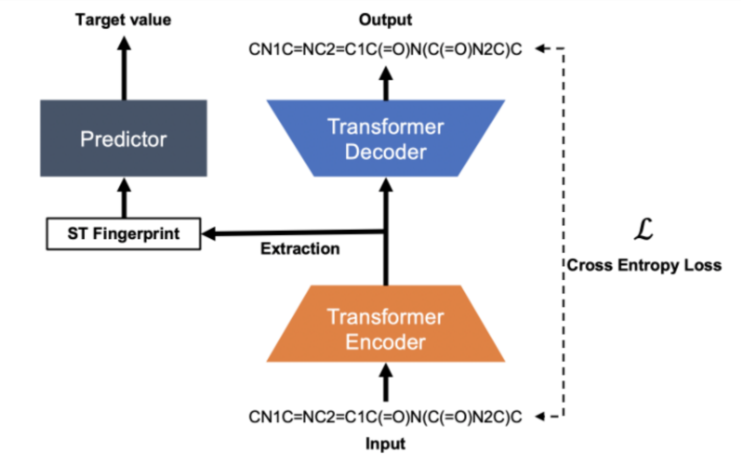
SMILES



N1CCN(CC1)C(C(F)=C2)=CC(=C2C4=O)N(C3CC3)C=C4C(=O)O

SMILES

SMILES Transformer: Pre-trained Molecular Fingerprint for Low Data Drug Discovery(2019)



MULTIMODAL MOLECULAR PRETRAINING VIA MODALITY BLENDING

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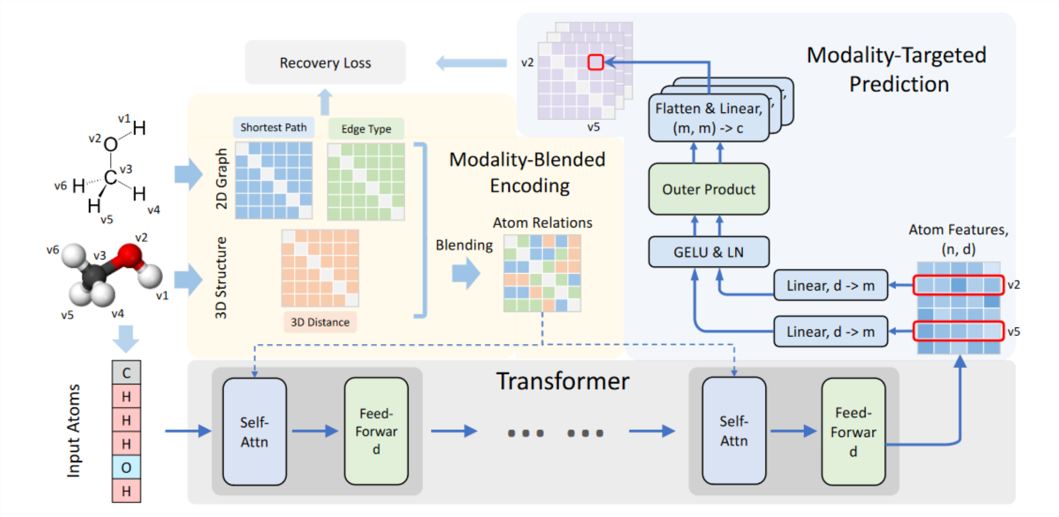
Illustration of unified molecular representation learning process



Modality-blended Encoding

Author adopts three appearances of relations across 2D and 3D modalities following **Transformer-M**.

- Ψ^{ij}_{SPD} represents the shortest path distance between atom i and j
- $\Psi^{ij}_{\mathrm{Edge}} = \frac{1}{N} \sum_{n=1}^{N} \mathbf{w}_n^\top \mathbf{e}_n$
- $\Psi^{ij}_{\mathsf{Distance}}$ is the encoding of Euclidean distances of an atom pair (i, j)

The blended matrix is determined as follows:

$$\Psi^{ij}_{\mathsf{2D\&3D}} = \Psi^{ij}_{\mathsf{SPD}} \mathbb{1}_1 + \Psi^{ij}_{\mathsf{Edge}} \mathbb{1}_2 + \Psi^{ij}_{\mathsf{Distance}} \mathbb{1}_3, \text{ where } \mathbb{1}_k = \begin{cases} 1 & \text{if } s^{ij} = k \\ 0 & \text{otherwise} \end{cases} \tag{1}$$

where each position (i, j) randomly selects its element from one of the $\Psi^{ij}_{\mathsf{SPD}}, \Psi^{ij}_{\mathrm{Edge}}, \Psi^{ij}_{\mathsf{Distance}}$

Modality-blended Encoding

Then inject this modality-blended relation $\Psi_{\mathbf{2D\&3D}}$ into the self-attention module:

$$\text{Attention}(\mathbf{Q}, \mathbf{K}, \mathbf{V}) = \text{softmax}\left(\frac{\mathbf{Q}\mathbf{K}^{\top}}{\sqrt{d}} + \Psi_{\mathbf{2D\&3D}}\right)\mathbf{V} \tag{2}$$

Modality-targeted Prediction

The model recovers the full $\mathcal{R}_{\mathrm{spd}}, \mathcal{R}_{\mathrm{edge}}, \mathcal{R}_{\mathrm{distance}}$.

- atom representations $\mathbf{X}^{L+1} \in \mathbb{R}^{n \times d}$
- two independent Linear layers $\mathbf{W}_L, \mathbf{W}_r \in \mathbb{R}^{m \times d}$
- modality-targeted head:$\mathbf{W}_{\mathrm{head}} \in \mathbb{R}^{c \times m^2}$
- $\mathrm{G}(\cdot) = \mathrm{LayerNorm}(\mathrm{GELU}(\cdot))$

$$\begin{aligned} \mathbf{o}_{ij} &= \mathrm{G}(\mathbf{W}_l \mathbf{X}_i^{L+1}) \otimes \mathrm{G}(\mathbf{W}_r \mathbf{X}_j^{L+1})^\top \in \mathbb{R}^{m \times m} \\ \mathbf{z}_{ij} &= \mathbf{W}_{\mathrm{head}} \cdot \mathrm{Flatten}(\mathbf{o}_{ij}) \in \mathbb{R}^c \end{aligned} \tag{3}$$

We now obtain the modality-targeted relation matrix $\mathbf{Z} \in \mathbb{R}^{n \times n \times c}$, where c depends on the targeted task

Fine-tuning

For scenarios where a large amount of 2D molecular graphs is available while 3D conformations are too expensive to obtain:

$$\mathcal{L}_{\mathrm{2D}} = \frac{1}{K}\sum_{k=1}^{K} \ell\left(f(\mathcal{R}^{k}_{\mathrm{spd}}, \mathcal{R}^{k}_{\mathrm{edge}}, \mathcal{V}^{k}), \mathrm{y}^{k}_{\mathrm{2D}}\right) \tag{4}$$

When it comes to scenarios where 3D information is obtained:

$$\begin{gathered}
\mathrm{Attention}(\mathbf{Q}, \mathbf{K}, \mathbf{V}) = \mathrm{softmax}\left(\frac{\mathrm{QK}^{\top}}{\sqrt{d}} + \Psi_{\mathrm{SPD}} + \Psi_{\mathrm{Edge}} + \Psi_{\mathrm{Distance}}\right)\mathrm{V} \\
\mathcal{L}_{3D} = \frac{1}{K}\sum_{k=1}^{K} \ell\left(f(\mathcal{R}^{k}_{\mathrm{spd}}, \mathcal{R}^{k}_{\mathrm{edge}}, \mathcal{R}^{k}_{\mathrm{distance}}, \mathcal{V}^{k}), \mathrm{y}^{k}_{\mathrm{3D}}\right)
\end{gathered} \tag{5}$$

Insights

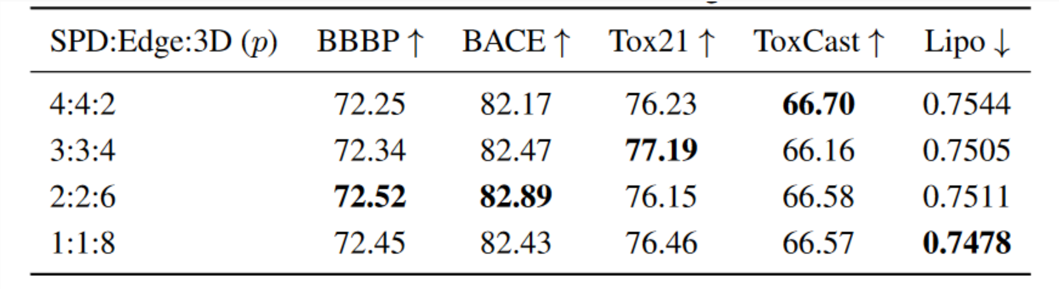
Consider two relations, denoted as $\mathcal{R}_{\text{2D}} = (a_{ij})_{n\times n}$ and $\mathcal{R}_{\text{3D}} = (b_{ij})_{n\times n}$,Their elements are randomly partitioned into two parts, represented as $\mathcal{R}_{\text{2D}} = [A_1, A_2], \mathcal{R}_{\text{3D}} = [B_1, B_2]$ The blended matrix is denoted as $\mathcal{R}_{\text{2D\&3D}} = [A_1, B_2]$.

- The training process with modality-blending maximizes the lower bound of the following mutual information:$I(A_2; A_1, B_2) + I(B_1; A_1, B_2)$
- The mutual information $I(A2; A1, B2) + I(B1; A1, B2)$ can be decomposed into two components below:

$$I(A_2;A_1,B_2)+I(B_1;A_1,B_2) = \frac{1}{2}[\underbrace{I(A_1;B_1)+I(A_2;B_2)}_{\textit{contrastive and generative}} + \underbrace{I(A_1;B_1|B_2)+I(A_2;B_2|A_1)}_{\textit{conditional contrastive and generative}}]$$

$$+\frac{1}{2}[\underbrace{I(A_1;A_2)+I(B_1;B_2)}_{\textit{mask-then-predict}} + \underbrace{I(A_1;A_2|B_2)+I(B_1;B_2|A_1)}_{\textit{multimodal mask-then-predict}}]$$

Experiments



SPD:Edge:3D (p)	BBBP ↑	BACE ↑	Tox21 ↑	ToxCast ↑	Lipo ↓
4:4:2	72.25	82.17	76.23	**66.70**	0.7544
3:3:4	72.34	82.47	**77.19**	66.16	0.7505
2:2:6	**72.52**	**82.89**	76.15	66.58	0.7511
1:1:8	72.45	82.43	76.46	66.57	**0.7478**

Figure 2: Ablations on the blending ratio