EQUIVARIANT ENERGY-GUIDED SDE FOR INVERSE MOLECULAR DESIGN

https://github.com/gracezhao1997/EEGSDE ICLR 2023

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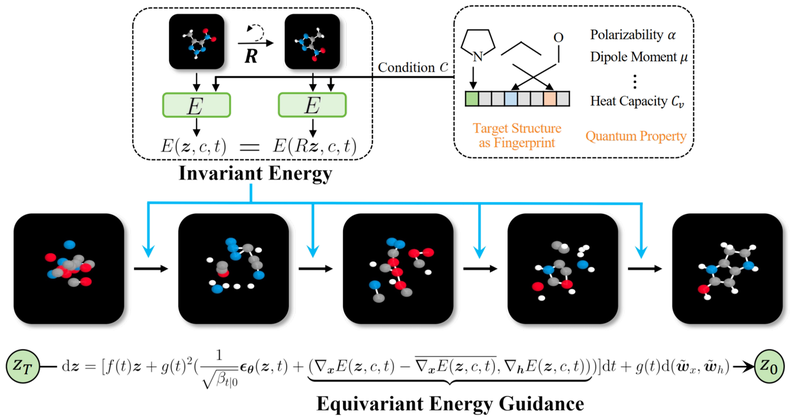
Motivation

- we propose equivariant energy-guided stochastic differential equations (EEGSDE), a flexible framework for controllable 3D molecule generation under the guidance of an energy function in diffusion models.



- Guide generated molecules towards desired properties c via a time-dependent energy function $E(z, c, t)$:

$$\mathrm{d}\boldsymbol{z} = [f(t)\boldsymbol{z} + g(t)^2(\frac{1}{\sqrt{\beta_{t|0}}}\boldsymbol{\epsilon}_{\boldsymbol{\theta}}(\boldsymbol{z}, t) + \underbrace{(\nabla_{\boldsymbol{x}} E(\boldsymbol{z}, c, t) - \overline{\nabla_{\boldsymbol{x}} E(\boldsymbol{z}, c, t)}, \nabla_{\boldsymbol{h}} E(\boldsymbol{z}, c, t))}_{\text{energy gradient taken in the product space}})]\mathrm{d}t + g(t)\mathrm{d}(\tilde{\boldsymbol{w}}_x, \tilde{\boldsymbol{w}}_h),\ \boldsymbol{z}_T \sim p_T(\boldsymbol{z}_T)$$

translational invariance

Rotation invariance:

Theorem 2. *Suppose the assumptions in Theorem 1 hold and $E(\boldsymbol{z}, c, t)$ is invariant to any orthogonal transformation $\boldsymbol{R}$, i.e., $E(\boldsymbol{R}\boldsymbol{x}, \boldsymbol{h}, c, t) = E(\boldsymbol{x}, \boldsymbol{h}, c, t)$. Then $p_{\boldsymbol{\theta}}(\boldsymbol{z}_0|c)$ is invariant to any rotational transformation.*

The EEGSDE defines a distribution $p(z_0|c)$ conditioned on the property c, which is invariant to translational and rotational transformations

Choice of Energy

➢ **Generating molecules with desired quantum property :**

- The energy function is defined as the squared error between the predicted property and the desired property:

time-dependent property prediction model; the desired property

$$E(\boldsymbol{z}_t, c, t) = s|g(\boldsymbol{z}_t, t) - c|^2$$

- Implementation of property prediction model :

$$g(\boldsymbol{z}_t, t) = \mathrm{Dec}(\mathrm{EGNN}^h(\boldsymbol{x}_t, \boldsymbol{h}'_t)), \quad \boldsymbol{h}'_t = \mathrm{concatenate}(\boldsymbol{h}_t, t)$$

the second component (h feature part) in the output of EGNN invariant to orthogonal transformations

EEGSDE is able to generate more accurate molecules than EDM

Method	MAE↓	Method	MAE↓
C_v ($\frac{\mathrm{cal}}{\mathrm{mol}}$K)		μ (D)	
U-bound	6.879±0.015	U-bound	1.613±0.003
#Atoms	1.971	#Atoms	1.053
Conditional EDM	1.065±0.010	Conditional EDM	1.123±0.013
EEGSDE (s=1)	1.037±0.010	EEGSDE (s=0.5)	0.930±0.005
EEGSDE (s=5)	0.981±0.002	EEGSDE (s=1)	0.858±0.006
EEGSDE (s=10)	**0.941**±0.005	EEGSDE (s=2)	**0.777**±0.007
L-bound	0.040	L-bound	0.043
$\Delta\varepsilon$ (meV)		$\varepsilon_{\mathrm{HOMO}}$ (meV)	
U-bound	1464±4	U-bound	645±41
#Atoms	866	#Atoms	426
Conditional EDM	671±5	Conditional EDM	371±2
EEGSDE (s=0.5)	574±4	EEGSDE (s=0.1)	357±4
EEGSDE (s=1)	542	EEGSDE (s=0.5)	320±1
EEGSDE (s=3)	**487**±3	EEGSDE (s=1)	**302**±2
L-bound	65	L-bound	39

➢ **Generating molecules with target structure** :

- The energy function is defined as the squared error between the predicted fingerprint and the molecule fingerprint :

target structure as fingerprint

molecular fingerprint

$$E(\boldsymbol{z}_t, c, t) = s\|m(\boldsymbol{z}_t, t) - c\|^2$$

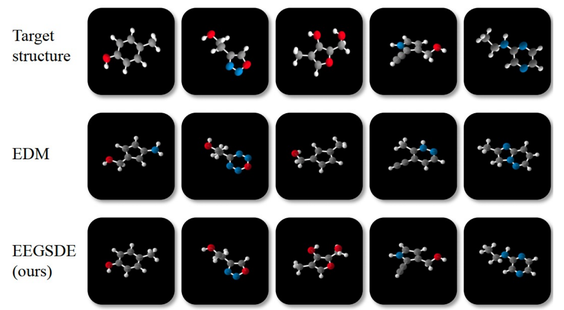
time-dependent fingerprint prediction model

- Implementation of fingerprint prediction model :

multi-label classifier

$$m(\boldsymbol{z}_t, t) = \sigma(\mathrm{Dec}(\mathrm{EGNN}^h(\boldsymbol{x}_t, \boldsymbol{h}'_t))), \quad \boldsymbol{h}'_t = \mathrm{concatenate}(\boldsymbol{h}_t, t)$$

EEGSDE better capture the structure information in molecules than EDM



EEGSDE has significantly better MAE on both properties than the conditional EDM

➢ **Generating molecules with multiple target properties:**

- EEGSDE is able to generate molecules targeted to multiple properties by combining the corresponding energy functions linearly:

$$E(\boldsymbol{z}_t, \boldsymbol{c}, t) = \sum_{k=1}^{K} E_k(\boldsymbol{z}_t, c_k, t)$$

Method	MAE1↓	MAE2↓
C_v ($\frac{\mathrm{cal}}{\mathrm{mol}}$K), μ (D)		
Conditional EDM	1.079±0.007	1.156±0.011
EEGSDE (s_1=10, s_2=1)	**0.981**±0.008	**0.912**±0.006
$\Delta\varepsilon$ (meV), μ (D)		
Conditional EDM	683±1	1.130±0.007
EEGSDE (s_1=s_2=1)	**563**±3	**0.866**±0.003
α (Bohr^3), μ (D)		
Conditional EDM	2.76±0.01	1.158±0.002
EEGSDE (s_1=s_2=1.5)	**2.61**±0.01	**0.855**±0.007