NEURAL INFORMATION PROCESSING SYSTEMS

MotiFlow | NEURIPS 2026 @ SYDNEY

3D Molecule Generation from Rigid Motifs via SE(3) Flows

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Generate 3D molecule from rigid motifs, not atoms.

One joint flow over motif types and their SE(3) poses.

SETUP	Following EDM [3], bonds are inferred from interatomic distances.
WORKS BEST	Medium and large drug-like molecules.
LIMITATIONS	Gains shrink for small or highly flexible molecules, which offer little rigid structure.

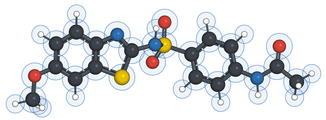
MCML MDS IMPERIAL

[1] Bose et al., ICLR 2024
SE(3)-stochastic flow matching for protein backbone generation

[2] Campbell et al., ICML 2024
Generative flows on discrete state-spaces

[3] Hoogeboom et al., ICML 2022
Equivariant diffusion for molecule generation in 3D

MOTIVATION Why rigid motifs? Molecules are built from rigid parts; explored in proteins but not yet in 3D drug-like molecules.



Atoms as 3D tokens

EDM · GEOLDM · END · VEDA

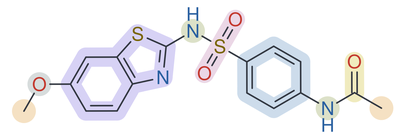
Every atom is a token, 44.4 on average in GEOM-Drugs; ring geometry is learned atom by atom.



Protein residues as rigid 3D frames

ALPHAFOLD2 · FRAMEDIFF · FOLDFLOW

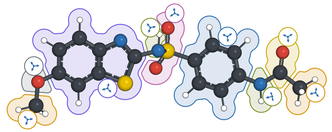
Every backbone residue is an SE(3) frame with a fixed vocabulary of 20 side-chains.



Motifs as 2D graphs

JT-VAE · HIERVAE · MOLER · MICAM

Chemically meaningful fragments, but generated as 2D graphs without any 3D geometry.



Motifs as rigid 3D frames

MOTIFLOW (THIS WORK)

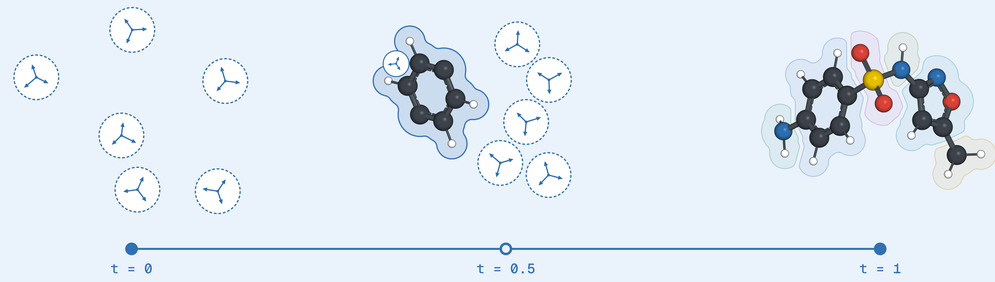
40 atoms → 9 motif tokens with SE(3) frames; inner geometry of every motif is exact.

METHOD How it works. Fragment once into a motif vocabulary, then generate molecules from pure noise.

REPRESENTATION



GENERATION



1 Rigid motifs

Keep planar rings, double and triple bonds and hydrogens; cut other bonds and split motifs below a frequency threshold α.

$$\mathcal{M} = \{(\mathbf{T}_k, m_k)\}_{k=1}^{K}$$
$$\mathbf{T}_k = (\mathbf{R}_k, \mathbf{x}_k) \in \mathrm{SE}(3)$$

2 Motif tokens

Each token pairs a vocabulary type with an SE(3) frame; a type stores its canonical pose, atom types and symmetries.

$$m_k = (\mathbf{P}_k, \mathbf{h}_k, \mathcal{S}_k) \in \mathcal{V}_m$$
$$\mathbf{P}_k \in \mathbb{R}^{N_k \times 3}, \quad \mathcal{S}_k \subset \mathrm{SO}(3)$$

3 Noise

Every motif type starts masked, rotations are drawn uniformly from SO(3) and translations from a Gaussian.

$$m_0 = [\mathrm{MASK}]$$
$$\mathbf{R}_0 \sim \mathcal{U}(\mathrm{SO}(3))$$
$$\mathbf{x}_0 \sim \mathcal{N}(\mathbf{0}, \mathbf{I})$$

4 Joint flow

Types unmask by a discrete flow [2] while frames follow SE(3) geodesics [1]; a single IPA network predicts both.

$$p_t(m_t \mid m_1) = (1-t)\,\delta_{[\mathrm{MASK}]} + t\,\delta_{m_1}$$
$$\mathbf{R}_t = \exp_{\mathbf{R}_0}\!\left(t \log_{\mathbf{R}_0} \mathbf{R}_1\right)$$
$$\mathbf{x}_t = (1-t)\,\mathbf{x}_0 + t\,\mathbf{x}_1$$

5 Exact lift

Atoms follow from placing the canonical pose of every motif in its frame, with no learned decoder or assembly.

$$\mathbf{Y}_k = \mathbf{P}_k \mathbf{R}_k + \mathbf{1}\,\mathbf{x}_k^{\top}$$
$$\mathbf{Y}_k \in \mathbb{R}^{N_k \times 3}, \quad k = 1, \ldots, K$$

RESULTS More stable drug-like molecules, from fewer and faster sampling steps.

95.0% stable atoms

on GEOM-Drugs at 100 steps, 5.0 points above the strongest baseline, VEDA-E.

METHOD	STEPS	STABLE ATOMS, % ↑
MotiFlow	**100**	**95.0**
VEDA-E	100	90.0
END	100	87.2
GeoBFN	1000	85.6
EDM	250	85.4
GeoLDM	1000	84.4
EquiFM	—	84.1

80 85 90 95 100

3.5× faster

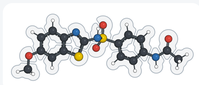
sampling than VEDA-E on QM9 at 50 steps, including the lift back to atoms.

METHOD	SECONDS, 50 STEPS ↓
QM9	
MotiFlow	**29.4**
GeoBFN	33.9
VEDA-E	102.3
END	155.2
GEOM-DRUGS	
MotiFlow	**100.7**
GeoBFN	213.3

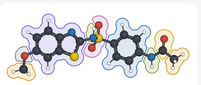
+10.6% atom stability

on QMugs from preserving rigid planar rings; same model and data, only the fragmentation differs.

NO RINGS · 15 MOTIFS



PLANAR RINGS · 9 MOTIFS



DATASET	STABLE ATOMS, % ↑	GAIN
GEOM-Drugs	86.7 → **95.0**	+8.3
QMugs	85.5 → **96.1**	+10.6

80 85 90 95 100

95.4% match

in atom composition on QM9, plus higher substructure similarity, with 5–10× fewer steps.

METHOD	STEPS	COMPOSITION, % ↑
cMotiFlow	**100**	**95.4**
cEND	500	91.5
cEDM	500	76.2

70 80 90 100

METHOD	STEPS	TANIMOTO ↑
cMotiFlow	**100**	**0.862**
cEND	1000	0.828
cEDM	1000	0.673

0.6 0.7 0.8 0.9