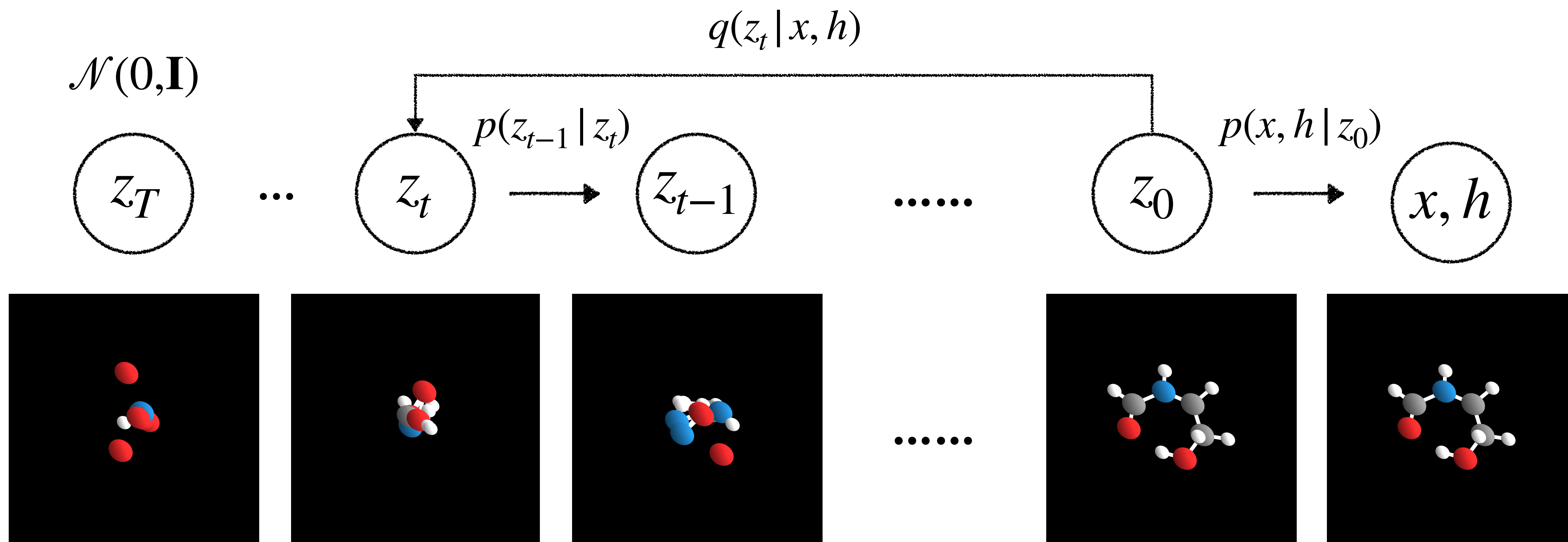


Learning Generative Dynamics for 3D Molecule Generation via Sequential Neuro-Symbolic Constraints

Zhuoran Li, Xu Sun, Chang Wen Chen, Wanyu Lin*

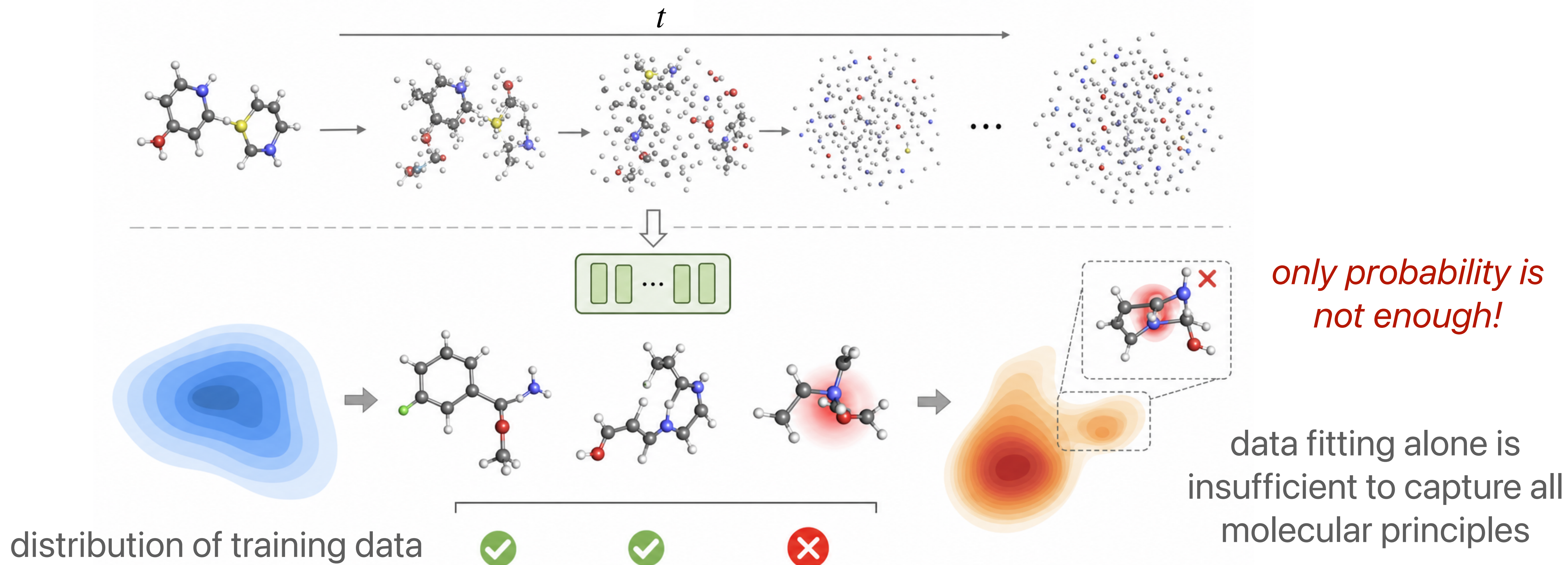
NeurIPS 2026

3D molecule generation with diffusion models



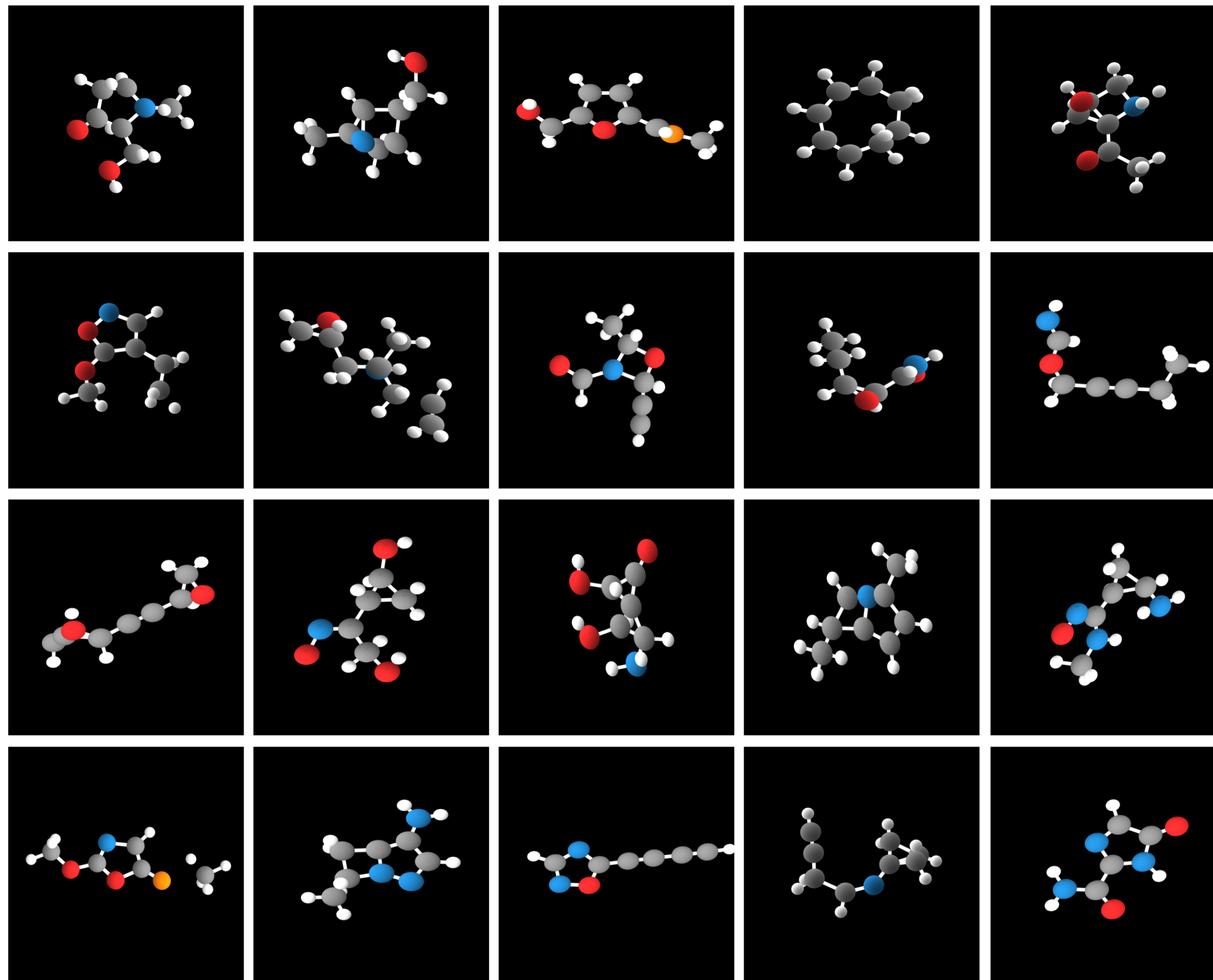
The network learns to denoise progressively noised molecular data, enabling molecule generation by iteratively recovering from pure Gaussian noise

Problem with diffusion-based molecule generation



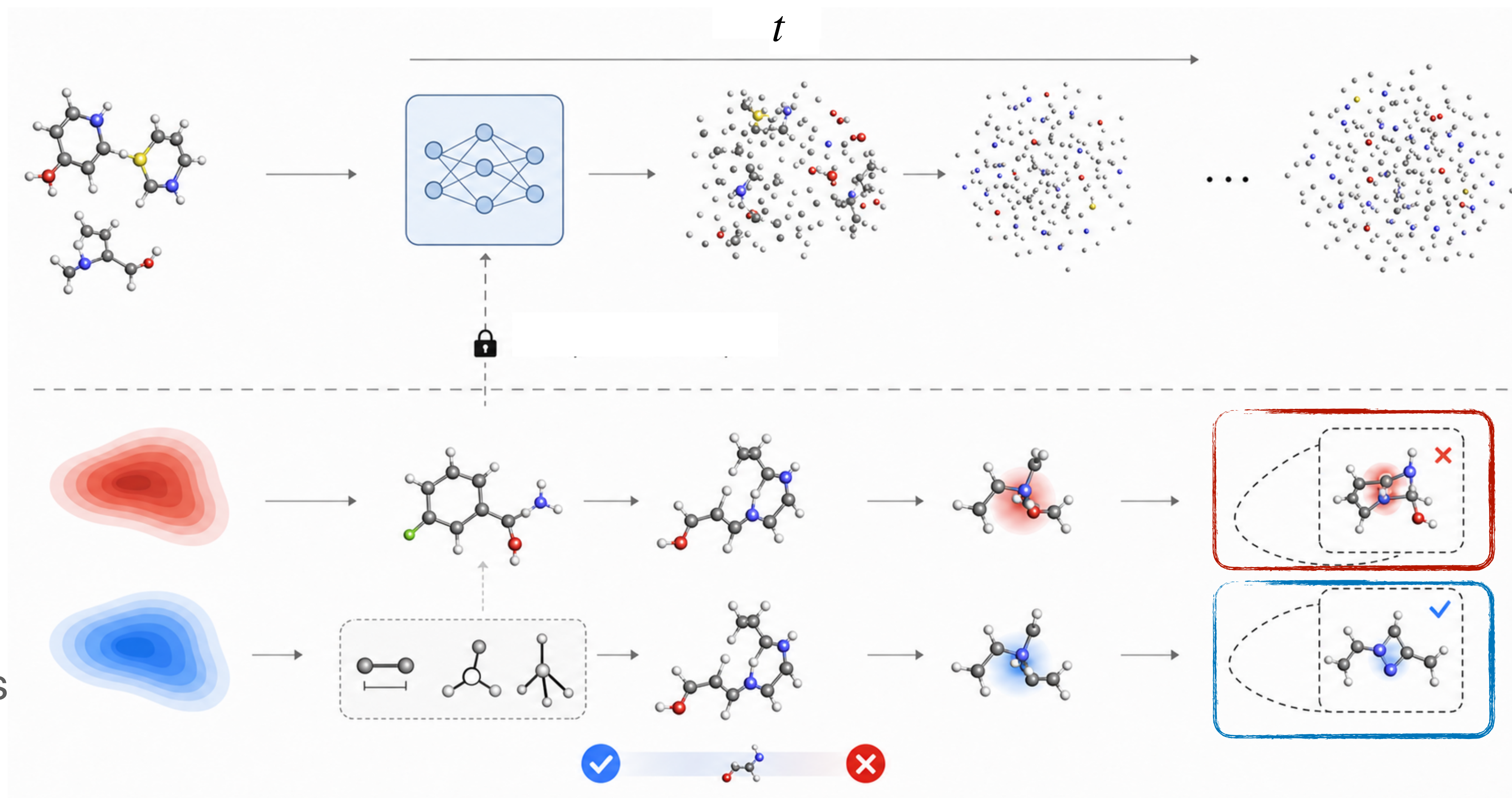
Generated samples can be statistically plausible yet chemically invalid, as distributional fit does not guarantee compliance with underlying chemical rules

Some examples of generation failures



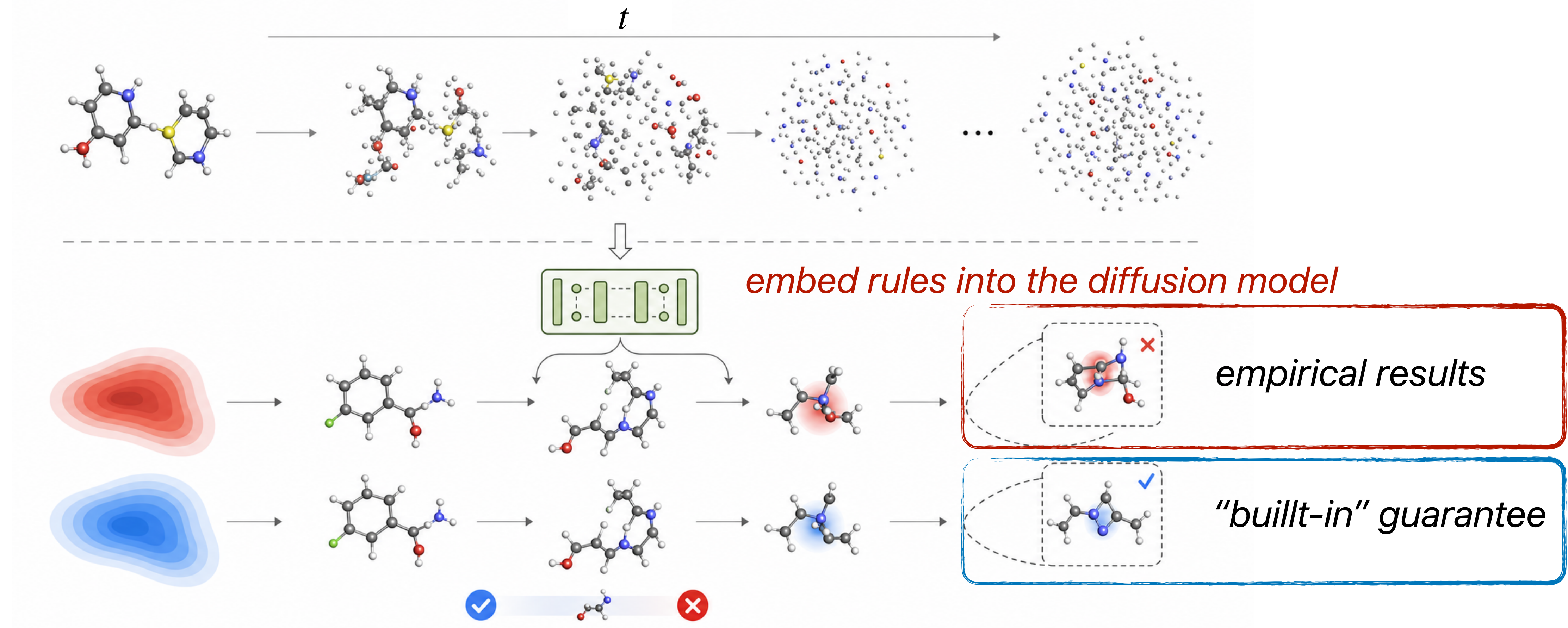
Diffusion models didn't learn the scientific rules explicitly during training

scientific rules are implicitly represented in the data



Embedding physicochemical priors into the generative process turns weak statistical cues into more reliable physicochemical enforcement

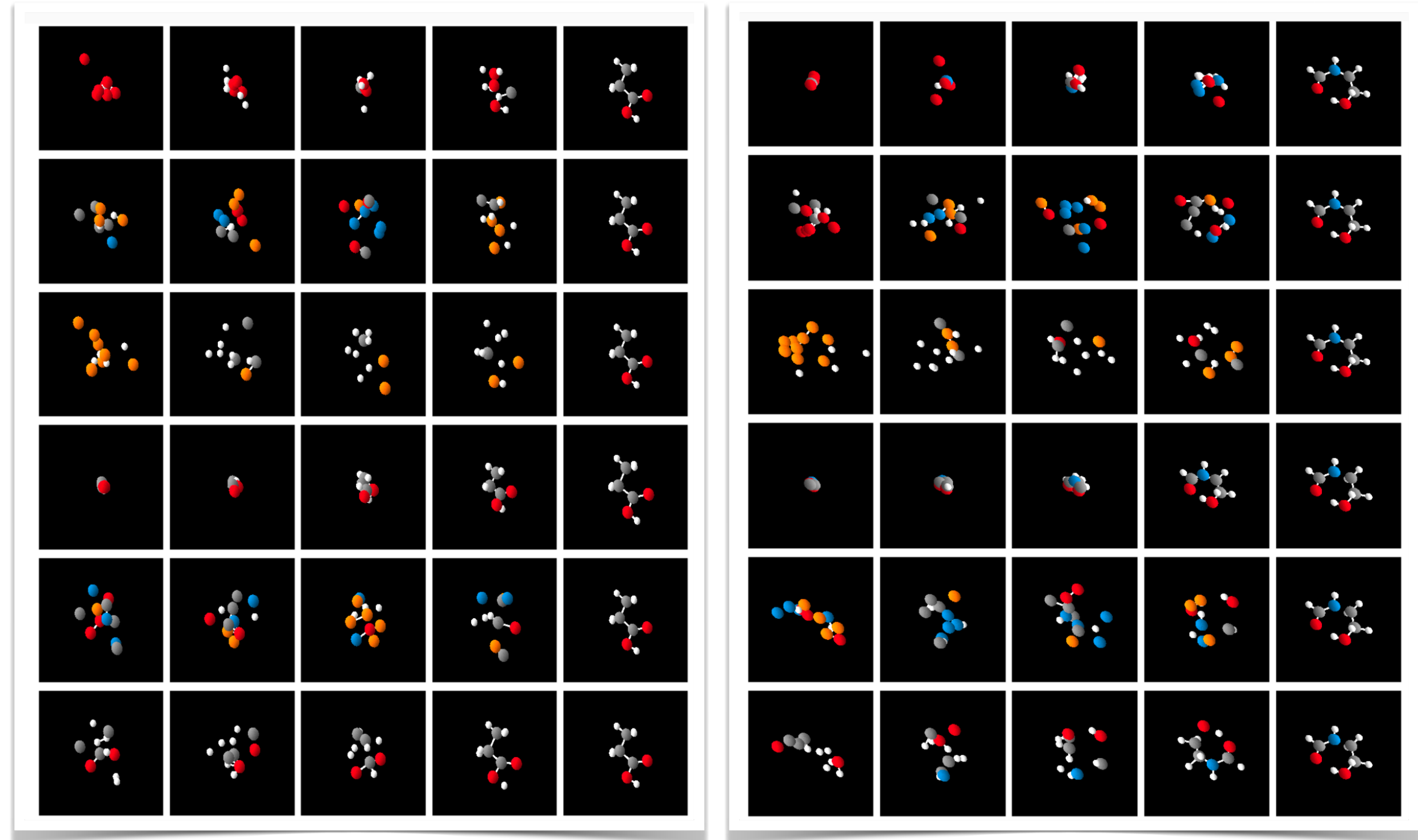
Our solution: learn the data distribution while explicitly capturing the **physicochemical rules**



We aim to find a way to directly encode the physicochemical rules into the diffusion training

How to design better constraint?

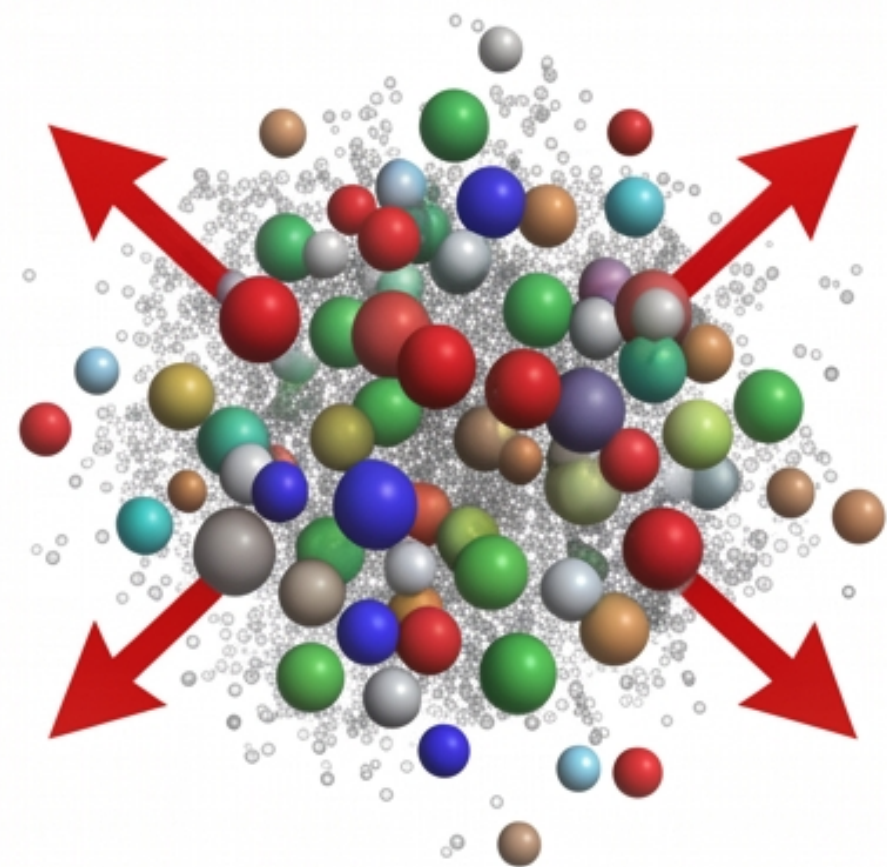
- ▶ Diffusion trajectory of 3D molecule generation exhibits a *coarse-to-fine evolution*.
- ▶ Valid molecules arise by first mitigating *macroscopic geometric* conflicts and then refining structures toward *microscopic consistency* through iterative denoising.



iterative denoising

Design of SensDiff: from global geometry to local consistency

Geometric Conflict

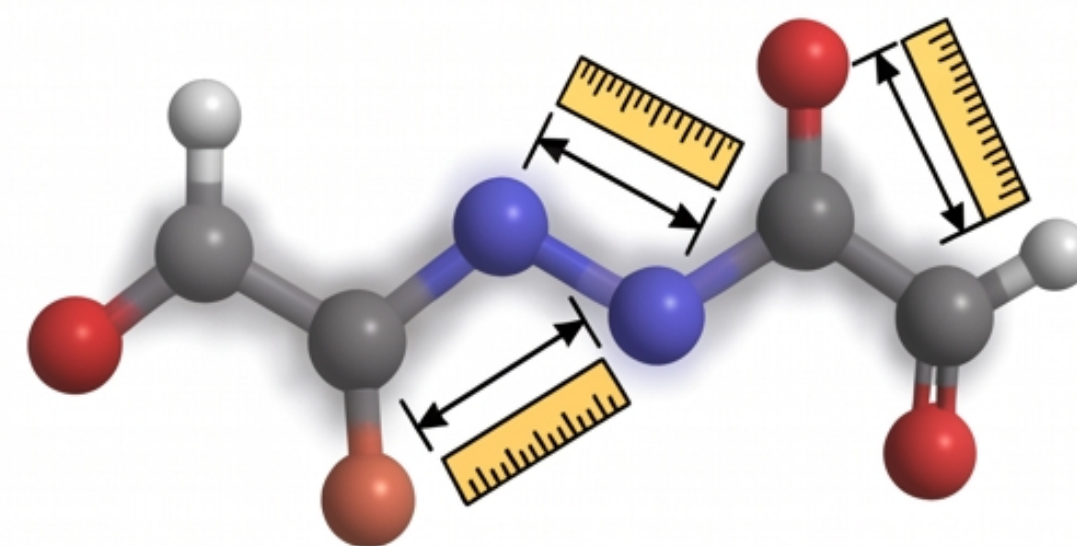


stage 1

Penalizes geometric clash by **enforcing a minimum distance** between non-bonded atoms

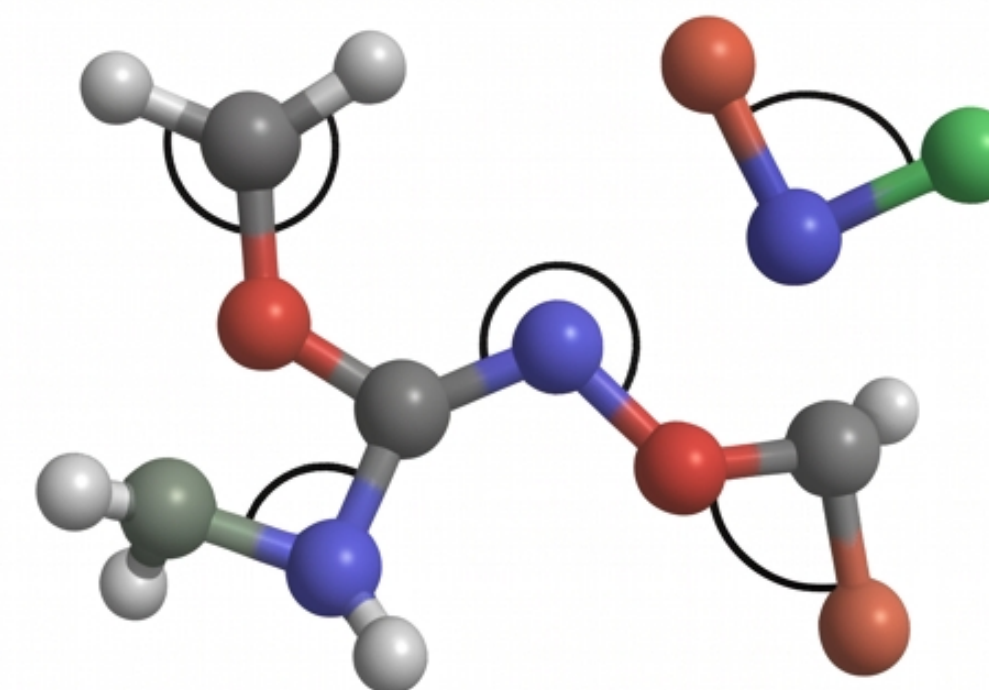
Enforces bond length consistency by **penalizing deviations** from expected bond distances

stage 2



Bond Length

Bond Angle

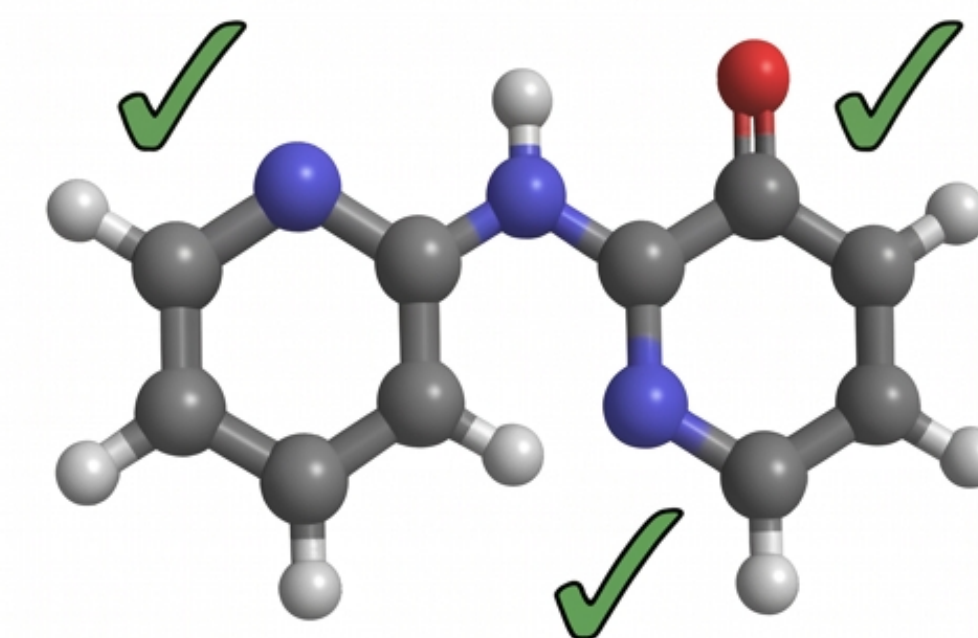


stage 3

Enforces bond angle consistency by **penalizing deviations** from expected bond angles

Penalizes valence assignments that violate the **admissible valence** of each atom

stage 4



Valence Validity

Training diffusion models with symbolic constraints

- ▶ The symbolic loss is defined as

$$\mathcal{L}_{\text{symbolic}}(e) = \lambda_c(e) \cdot E_{\text{clash}} + \lambda_b(e) \cdot E_{\text{bond_length}} + \lambda_a(e) \cdot E_{\text{bond_angle}} + \lambda_v(e) \cdot E_{\text{valence}}$$

- ▶ The final training objective is defined as

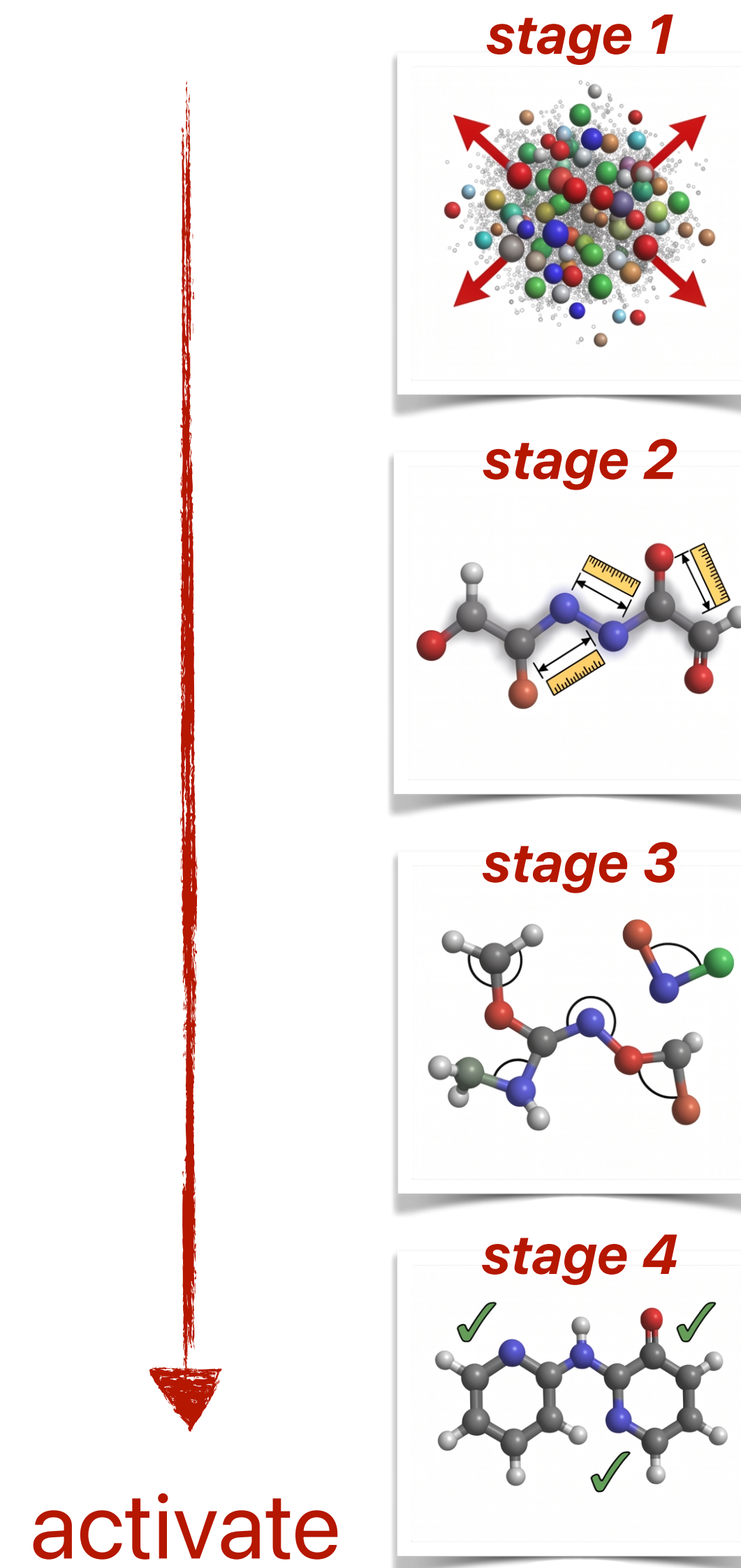
$$\mathcal{L}_{\text{total}}(e) = \mathcal{L}_{\text{diffusion}}(e) + \mathcal{L}_{\text{symbolic}}(e)$$

- ▶ Symbolic rules encode domain knowledge as differentiable penalties that guide denoising by penalizing invalid intermediates during training.
- ▶ The model is encouraged not merely to learn the observed atomic distribution, but to shape its generative dynamics around physicochemical rules.

Strategies to stabilize the diffusion training

Intuition: not all constraints should apply to the diffusion model with the same strength at the same time.

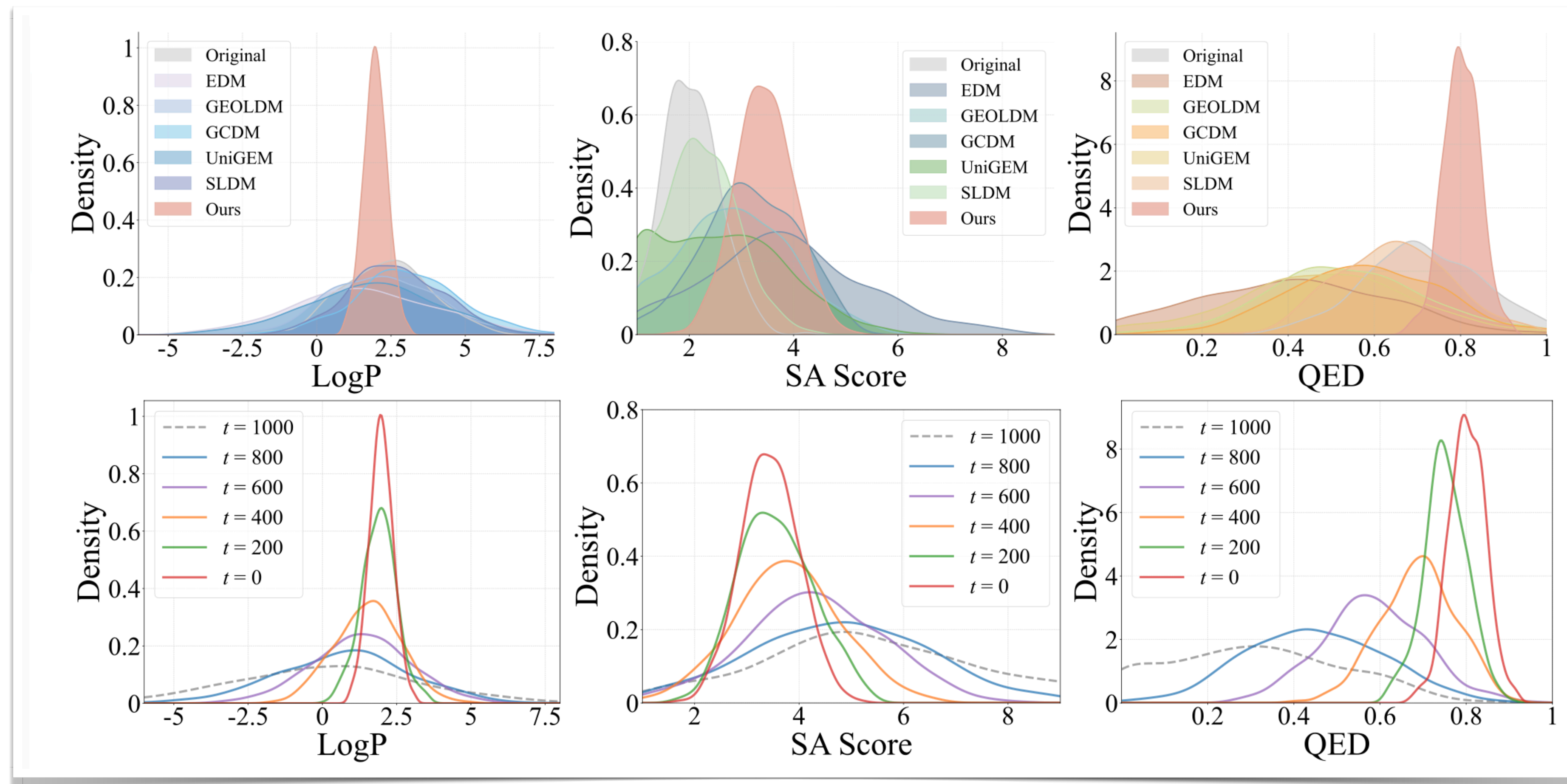
- ▶ **When to activate:** only when the intermediate denoised state is sufficiently stable, the corresponding constraints provide a meaningful training signal.
- ▶ **With what strength:** whether the weights are "fully applied" depends on the model's satisfaction of the constraint.



Experimental results: unconditional generation

Model	QM9 Valid	QM9 Atom Sta	QM9 Mol Sta	QM9 Valid & Unique	GEOM-Drugs Valid	GEOM-Drugs Atom Sta
EDM	87.9	95.5	78.4	96.0	88.8	77.5
EEGSDE	89.8	95.7	80.3	94.3	89.1	79.1
GEOLDM	89.8	94.2	86.2	95.5	95.6	80.7
EquiFM	91.6	94.4	84.3	94.7	95.7	80.3
GeoBFN	90.7	94.9	86.9	93.3	88.5	81.5
GCDM	91.4	94.2	82.5	95.7	91.2	84.5
RADM	90.0	95.9	84.7	92.2	95.7	82.1
SLDM	92.1	95.0	90.9	89.1	95.8	84.8
UAE-3D	94.4	96.2	95.4	94.4	84.4	82.5
UniGEM	92.0	95.2	87.1	93.5	94.7	82.1
SensDiff (Ours)	96.9	98.1	95.6	97.2	97.2	87.9

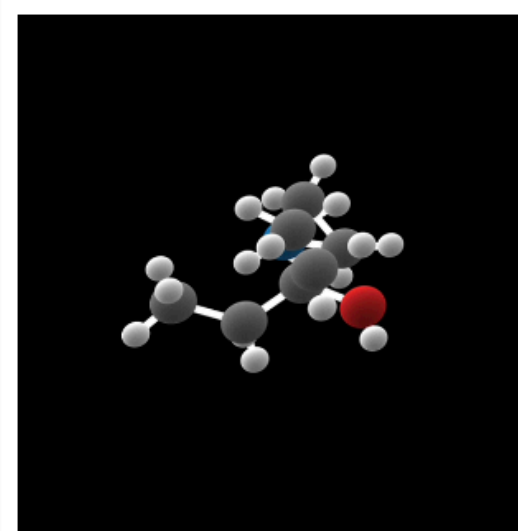
Experimental results: conditional generation with drug properties



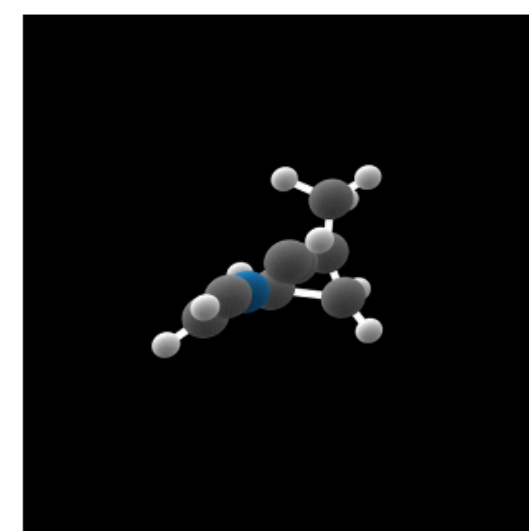
The generated molecules precisely satisfy the specified drug-design constraints and they converge to the target values over the denoising steps

Experimental results: conditional generation with quantum chemical properties

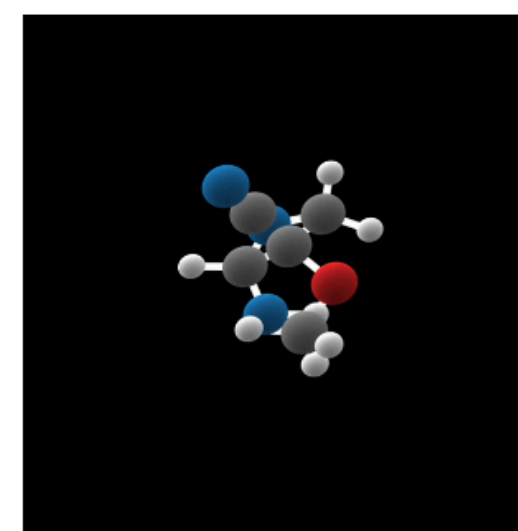
Model	C_v (cal/mol·K)	μ (D)	α (Bohr ³)	$\Delta\varepsilon$ (meV)	$\varepsilon_{\text{HOMO}}$ (meV)	$\varepsilon_{\text{LUMO}}$ (meV)
EDM	1.154	1.164	2.87	676	368	603
EEGSDE	0.986	0.812	2.61	506	314	462
GEOLDM	1.072	1.156	2.46	608	351	541
EquiFM	1.081	1.148	2.52	614	349	548
GeoBFN	0.992	1.041	2.43	596	339	532
GCDM	0.723	0.879	2.06	624	357	495
RADM	0.907	0.851	2.07	474	301	397
SLDM	0.781	0.831	1.53	456	331	362
UAE-3D	0.582	0.638	1.61	327	224	259
UniGEM	0.754	0.801	1.84	441	295	349
SensDiff (Ours)	0.569	0.618	1.49	314	219	246



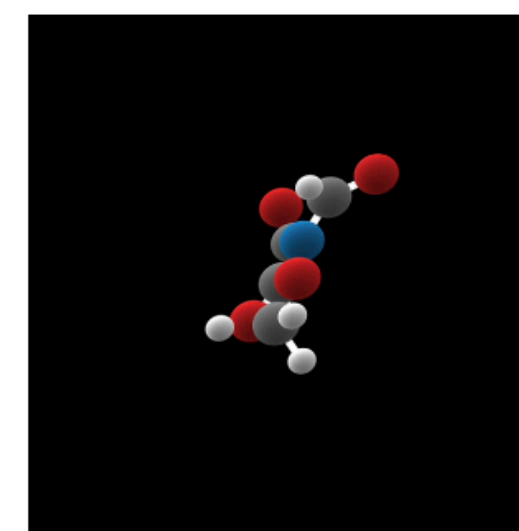
$\alpha = 59.8$
 $\mu = 0.18$



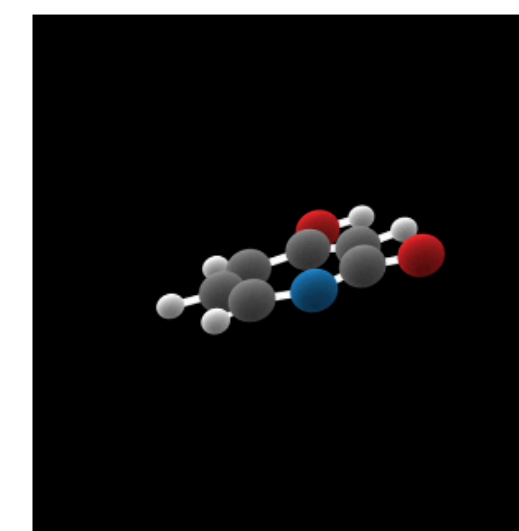
$\alpha = 59.8$
 $\mu = 2.21$



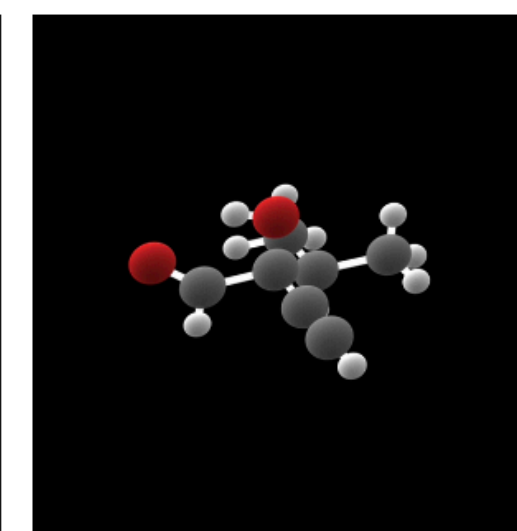
$\alpha = 59.8$
 $\mu = 16.17$



$\varepsilon_{\text{LUMO}} = 0.04$
 $C_v = 36.26$

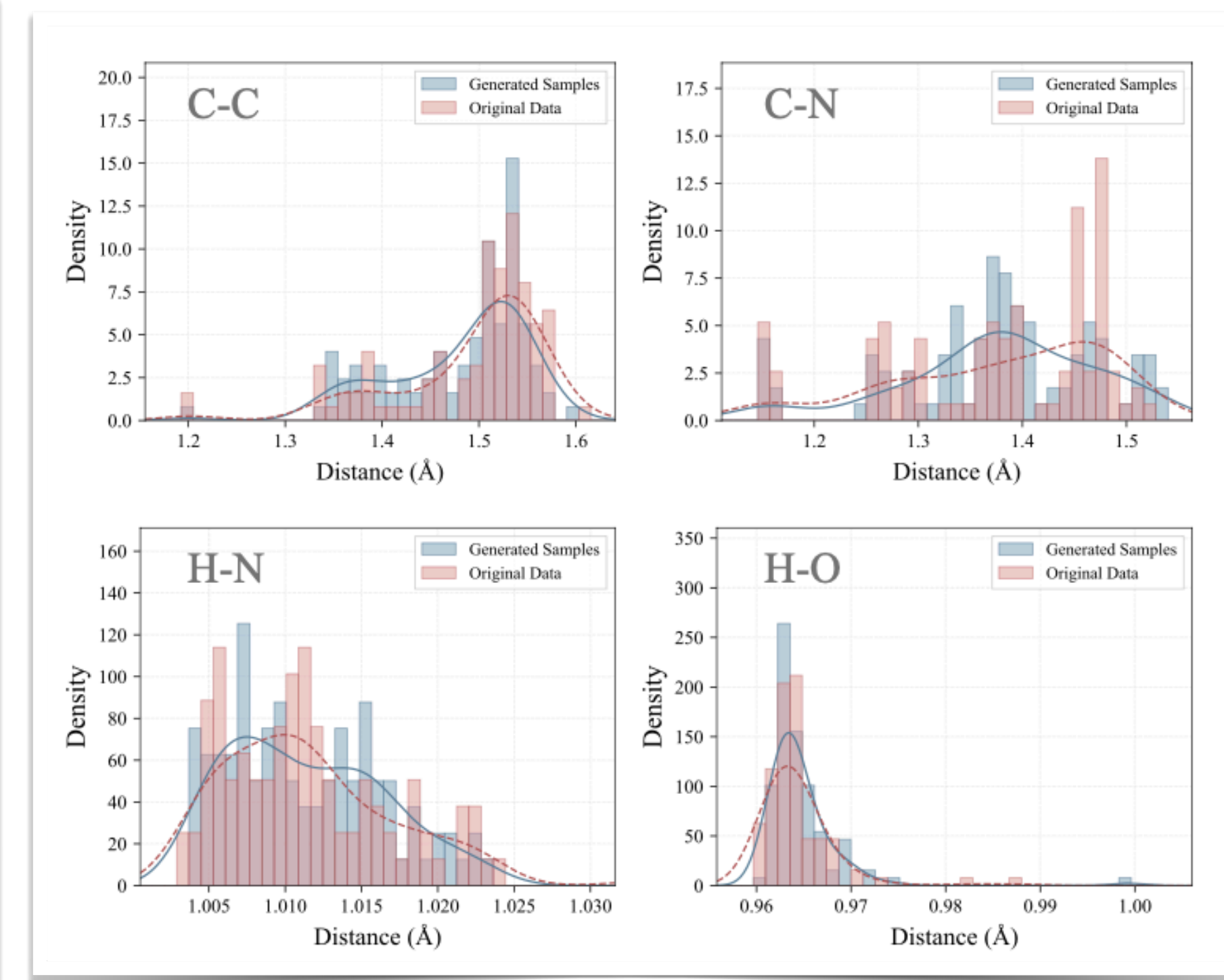
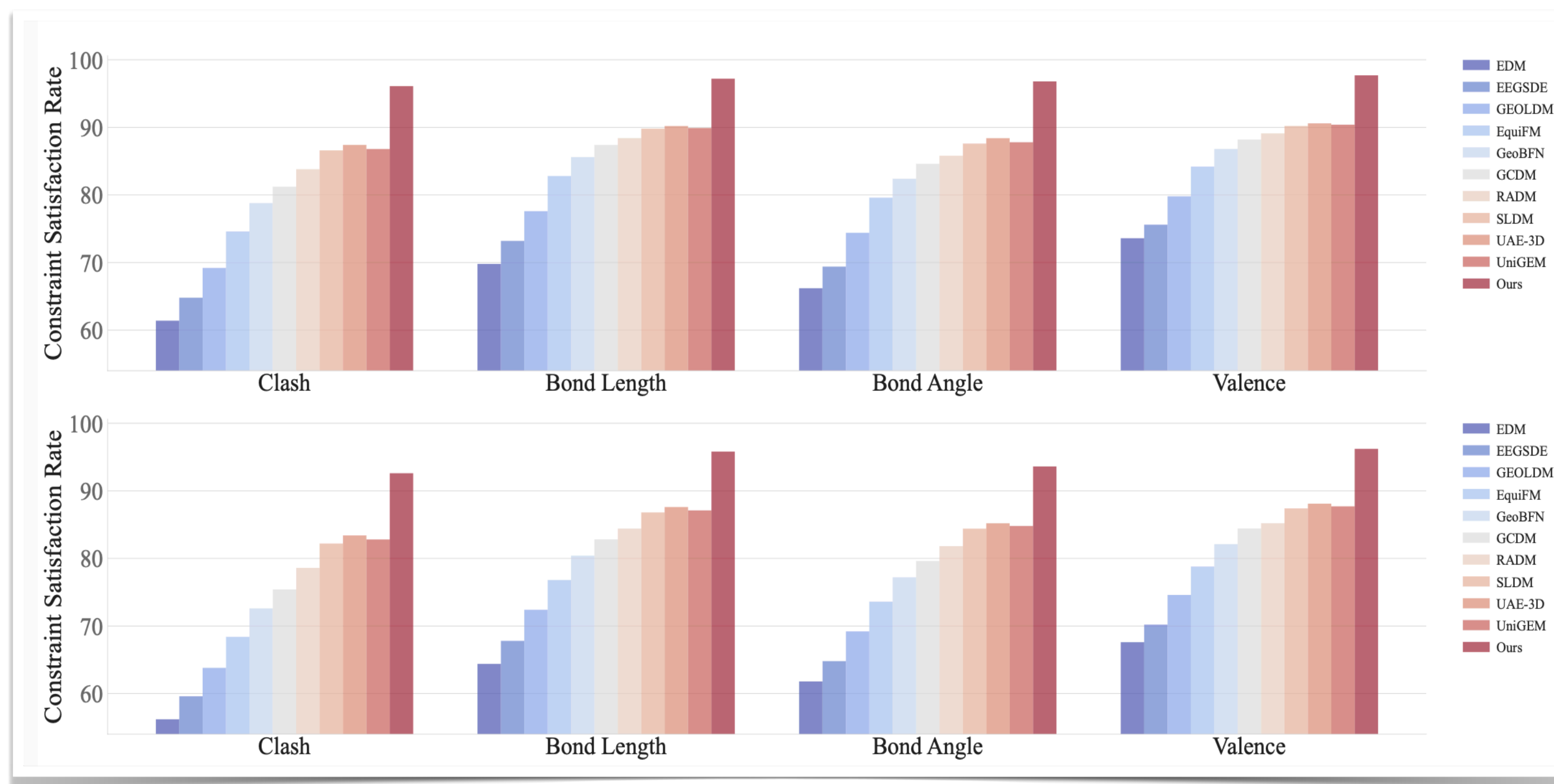


$\varepsilon_{\text{LUMO}} = 0.04$
 $C_v = 25.49$



$\varepsilon_{\text{LUMO}} = 0.04$
 $C_v = 11.94$

Experimental results: constraint satisfaction



Our method achieves the best constraint satisfaction while preserving geometrically plausible bond distributions

Key empirical insights

- ▶ The neuro-symbolic approach provides an interpretable lens for *model design* by exposing violated rules and enabling targeted fixes.
- ▶ SensDiff directly encodes rules into its generative dynamics, learning scientific principles that *generalize to unseen data*.
- ▶ The integration of physicochemical priors enables our approach to *internalize domain knowledge*, grounding opaque neural denoising in scientific principles.



Thank you