Conditional Synthesis of 3D Molecules with Time Correction Sampler

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The Challenge of Targeted Molecule Design

- Discovering novel molecules with specific properties is crucial for drug discovery and materials science.
- Existing conditional generation methods often struggle to balance target property matching with generating valid and stable molecular structures.

Online Guidance: Training-Free Property Control

- Online Guidance (OG): Recent approaches like DPS (Chung et al, 2022) enable conditional diffusion without labeled pairs $(\mathbf{x}_t, \mathbf{c})$.
  - **Approximate Conditional Score Estimation**: $\nabla_{x_t} \log p(x_t \mid c) \approx \nabla_{x_t} \log p(c \mid \hat{x}_0)$ using Tweedie's Formula for $\hat{x}_0$.
  - LGD (Song et al, 2023) further refines this by Monte Carlo sampling $\mathbf{x}_0$ from $q(\mathbf{x}_0 \mid \mathbf{x}_t) = N(\hat{\mathbf{x}}_0, \sigma_t^2)$, providing an average over $\mathbf{x}_0^i$ samples:

$$\nabla_{\mathbf{x}_t} \log \left(\mathbb{E}_{\mathbf{x}_0 \sim p(\mathbf{x}_0 \mid \mathbf{x}_t)} p(\mathbf{c} \mid \hat{\mathbf{x}}_0) \right) \approx \nabla_{\mathbf{x}_t} \log \left(\frac{1}{m} \sum_{i=1}^{m} \exp\left(-\mathscr{L}(\mathscr{A}(\mathbf{x}_0^i), \mathbf{c})\right) \right) := \mathbf{g}(\mathbf{x}_t, t)$$

where $\mathscr{A}$ is a property estimator satisfying $\mathbf{c} = \mathscr{A}(\mathbf{x}_0)$.

  - **Guidance Incorporation**:

$$\mathrm{d}\mathbf{x}_t = \left[-\frac{1}{2}\beta(t)\mathbf{x}_t - \beta(t)(\nabla_{\mathbf{x}_t} \log p_t(\mathbf{x}_t) + z\mathbf{g}(\mathbf{x}_t, t) \right] \mathrm{d}t + \sqrt{\beta(t)}\mathrm{d}\bar{\mathbf{w}}_t$$

- However, OG can push samples off the correct data manifold, leading to unstable and invalid molecules.

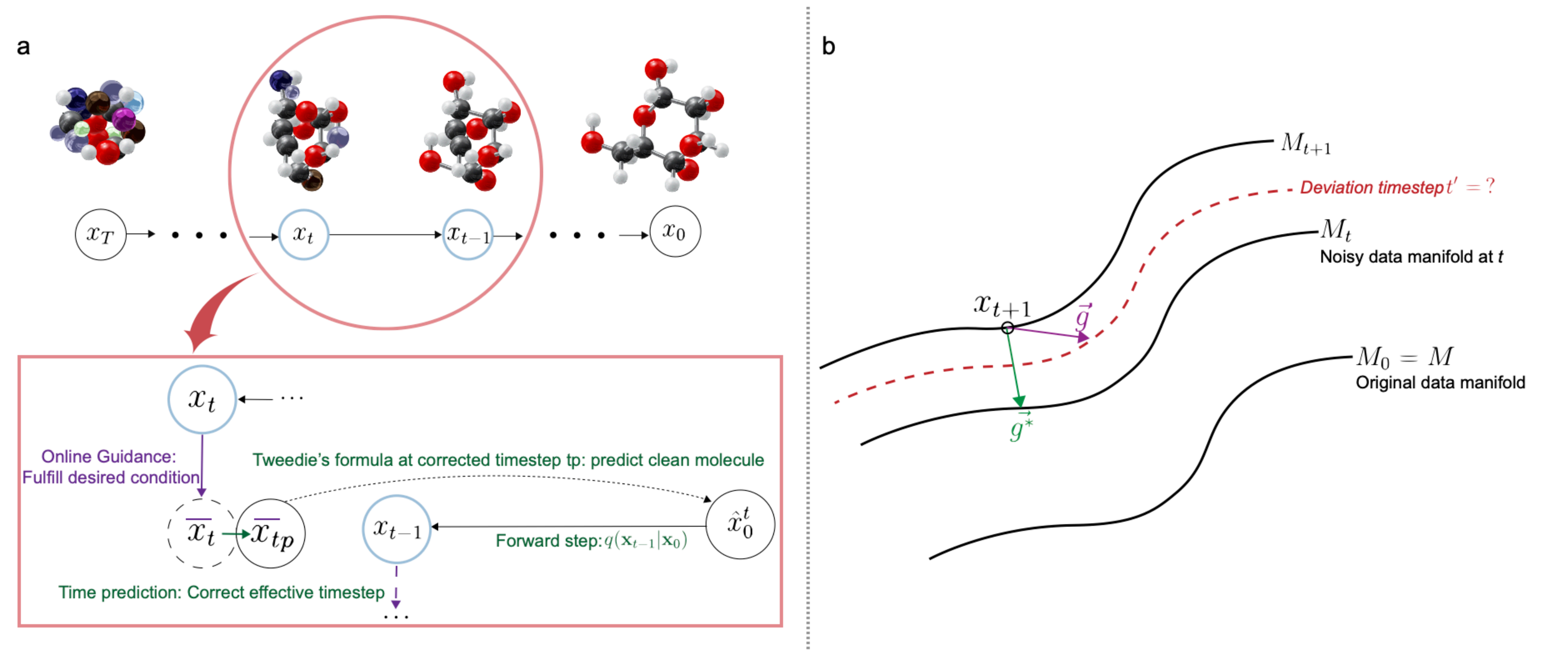
Time Correction Sampler: Staying on Track

- Our novel Time Correction Sampler (TCS) addresses OG's limitations:
  1. A trained Time Predictor, $\phi(x_t)$, predicts the effective timestep t_p of a given noisy sample x_t.
  2. Time Correction: We modify Tweedie's formula using t_p:

$$f(\tilde{x}_t, t_p) = \frac{\tilde{x}_t + (1 - \bar{\alpha}_{t_p}) S_\theta(\tilde{x}_t, t_p)}{\sqrt{\bar{\alpha}_{t_p}}}$$

  3. The corrected sample is then perturbed back to the correct timestep $t - 1$ using the forward process.
- TCS ensures that generated samples remain consistent with the learned data distribution.

Time-Aware Conditional Synthesis (TACS)



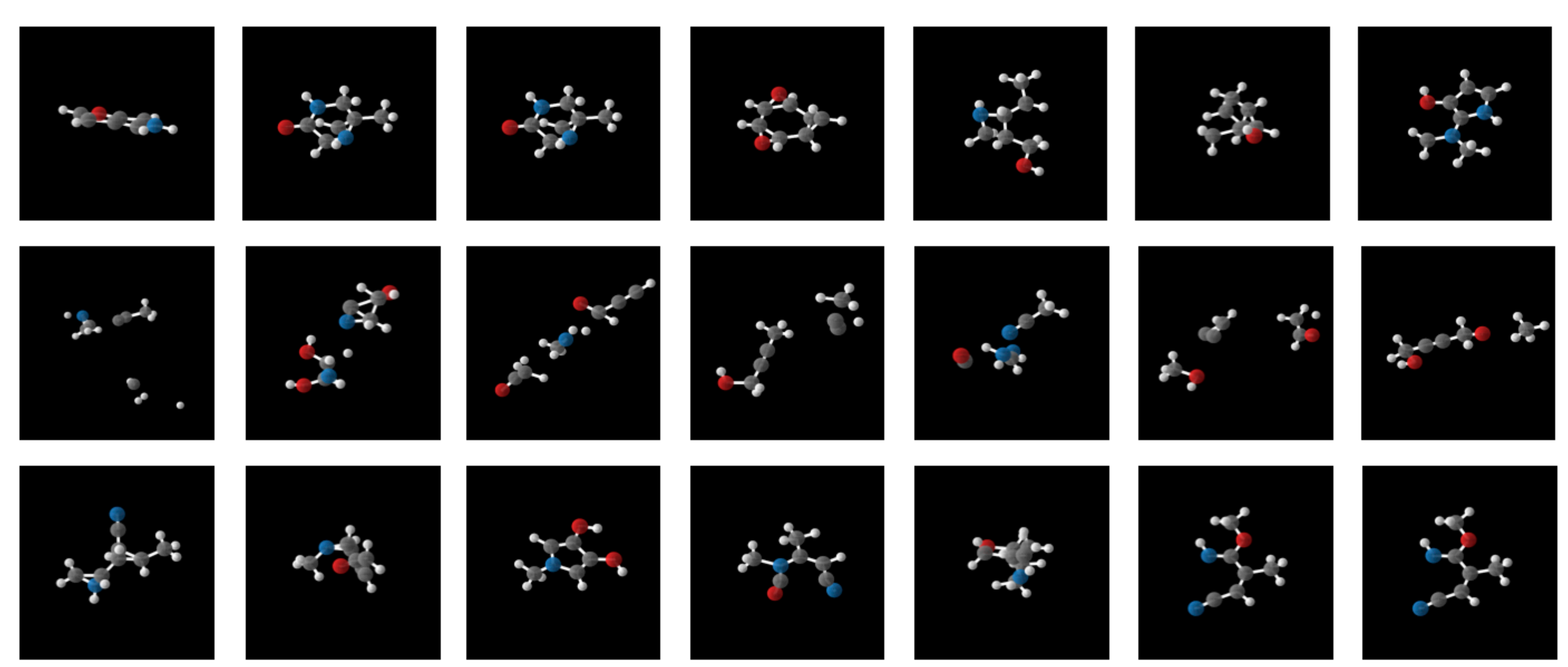
Overview of Time-Aware Conditional Synthesis (TACS).

- TACS integrates OG and TCS for effective conditional generation:
  1. Apply OG to guide the sample towards the target properties c.
  2. Use the Time Predictor to estimate the effective timestep t_p.
  3. Apply Time Correction to ensure the sample stays on the correct manifold.
  4. Iterate through the reverse diffusion process.

Algorithm 1 Time-Aware Conditional Synthesis (TACS)

Input: Total number of diffusion timesteps T, online guidance strength z, target condition $\boldsymbol{c}$, diffusion model $\boldsymbol{\theta}$, time predictor ϕ, time-clip window size Δ.

$\mathbf{x}_T \sim \mathcal{N}(0, \mathbf{I}_d)$
for $t = T$ to 1 **do**
  if Online guidance **then**
    $\mathbf{g}(\mathbf{x}_t, t) = -\nabla_{\mathbf{x}_t} \mathcal{L}(\mathcal{A}(\mathbf{x}_0), \mathbf{c})$ ▷ Online guidance from Eq. (8)
    $\mathbf{x}_t' \leftarrow \mathbf{x}_t + z \cdot \mathbf{g}(\mathbf{x}_t, t)$
    $t_{\text{pred}} \leftarrow \arg\max(\phi(\mathbf{x}_t'))$
    $t_{\text{pred}} \leftarrow \texttt{clip}(t_{\text{pred}}, \Delta)$
    $\hat{\mathbf{x}}_0' \leftarrow \texttt{Tweedie}(\mathbf{x}_t', t_{\text{pred}})$ ▷ from Eq. (11)
    $\mathbf{x}_{t-1} \leftarrow \texttt{forward}(\hat{\mathbf{x}}_0', t-1)$ ▷ from Eq. (1)
  else
    $\mathbf{x}_{t-1} \leftarrow \texttt{reverse}(\mathbf{x}_t, t)$ ▷ one reverse step by diffusion model
  end if
end for

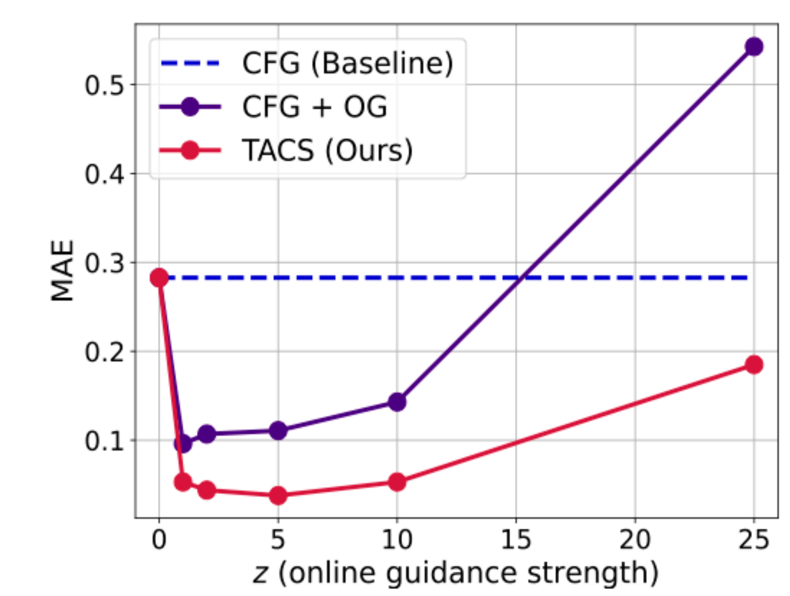


Visualization of molecules generated by TCS (top), online guidance (middle), and TACS (bottom).

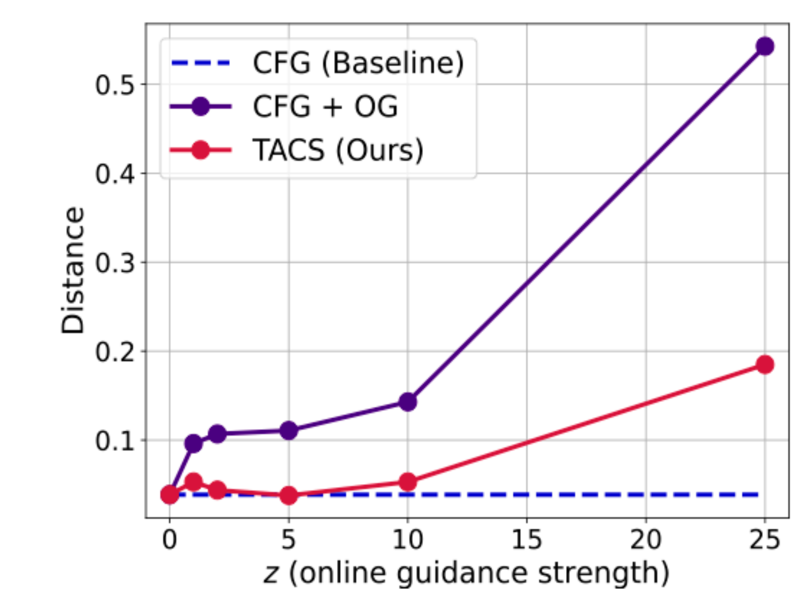
Synthetic Experiment with H_3^+

- The Quantum ML algorithm (VQE) calculates ground state energies for to H_3^+ providing conditional labels that leverage exact calculations for a given estimate.
  - Ground State Energy: $E_0 \leq \dfrac{\langle \psi(\boldsymbol{\theta}) \mid \hat{H} \mid \psi(\boldsymbol{\theta}) \rangle}{\langle \psi(\boldsymbol{\theta}) \mid \psi(\boldsymbol{\theta}) \rangle}$
  - Zeroth-Order Gradient:

$$\nabla_{\mathbf{x}_t} \log \mathbb{E}_{\mathbf{x}_0 \sim p(\mathbf{x}_0 \mid \mathbf{x}_t)} p(\mathbf{c} \mid \hat{\mathbf{x}}_0) \approx -\nabla_{\mathbf{x}_t} E_0(\hat{\mathbf{x}}_0^i) \approx -\sum_{i=1}^{k} \frac{E_0(\hat{\mathbf{x}}_0^i + \boldsymbol{h}_i) - E_0(\hat{\mathbf{x}}_0^i - \boldsymbol{h}_i)}{2\boldsymbol{h}_i}$$



Low MAE



Adhere to the data distribution

QM9 Dataset Experiment

Method	Δϵ (meV) MAE	MS (%)	Valid (%)
U-bound	1464±4	-	-
EDM	673±7	81.8±0.5	90.9±0.3
EEGSDE	539±5	80.1±0.4	90.5±0.3
OG	**95.2**±4	31.3±0.7	61.9±3.4
TCS(ours)	594±4	**91.9**±0.4	**96.0**±0.2
TACS(ours)	**332***±3	88.8±0.6	93.9±0.3
L-bound	65	-	-

Table1: Target Quantum Property

Method	QM9 Similarity ↑	MS (%)
cG-SchNet	0.499±0.002	-
Conditional EDM	0.671±0.004	-
TCS (Ours)	**0.792±0.077**	90.42
TACS (Ours) ($z = 0.01$)	0.694±0.001	**90.45**
TACS (Ours) ($z = 0.05$)	0.695±0.003	90.02
TACS (Ours) ($z = 0.1$)	0.713±0.087	90.28
EEGSDE ($s = 0.1$)	0.547±0.002	74.07
EEGSDE ($s = 0.5$)	0.600±0.002	74.67
EEGSDE ($s = 1.0$)	0.540±0.029	90.44

Table2: Target Structure

- TACS achieves the **lowest MAE** with **high molecular stability** and validity, consistently reaching the Pareto front by balancing stability and precise property targeting.