MacroGuide: Topological Guidance for Macrocycle Generation

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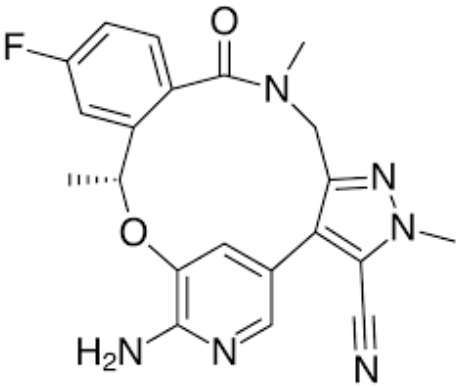
Why macrocycles?



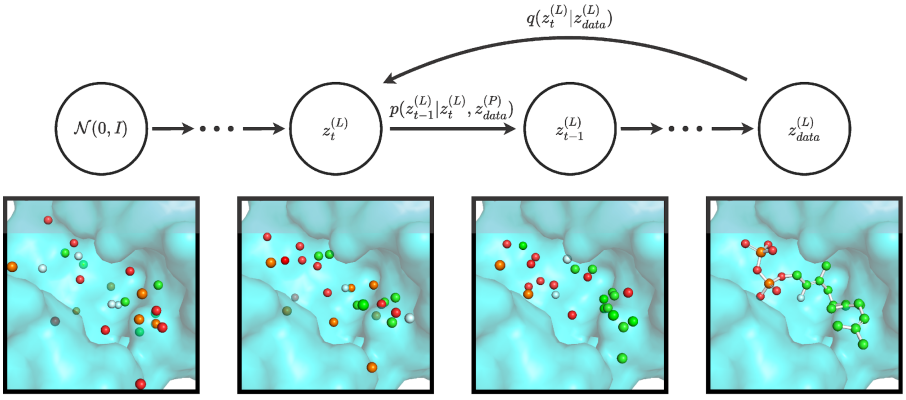
lorlatinib

- Macrocycles: ≥ 12 heavy atoms in a ring
- Good drug candidates
  - Better binding affinity
  - Higher selectivity
- Not just cyclic peptides

Why is it hard?

- **Data scarcity**
  - 30–40k macrocycles vs millions of small molecules
- **Global topology vs local validity**
  - "there exists a 12-cycle" is not a local property
  - classical generative models miss it

Background: Diffusion models



- **Forward:** noise the data progressively until pure Gaussian
- **Reverse:** a network learns the score

$$s_\theta(x_t, t) \approx \nabla_{x_t} \log p_t(x_t)$$

Image reproduced from [1]

Background: Persistent homology

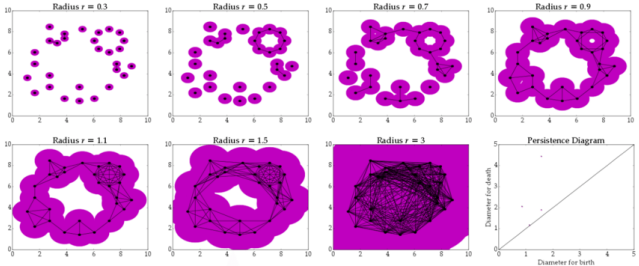


Image reproduced from [2]

- Atom positions $X \subset \mathbb{R}^3$
- Vietoris–Rips filtration on X
- Record birth and death of components
- H_0 = clusters of atoms
- H_1 = rings
- H_2 = cavities
- Differentiable! Two atoms contributing to each birth/death event

Apply guidance.

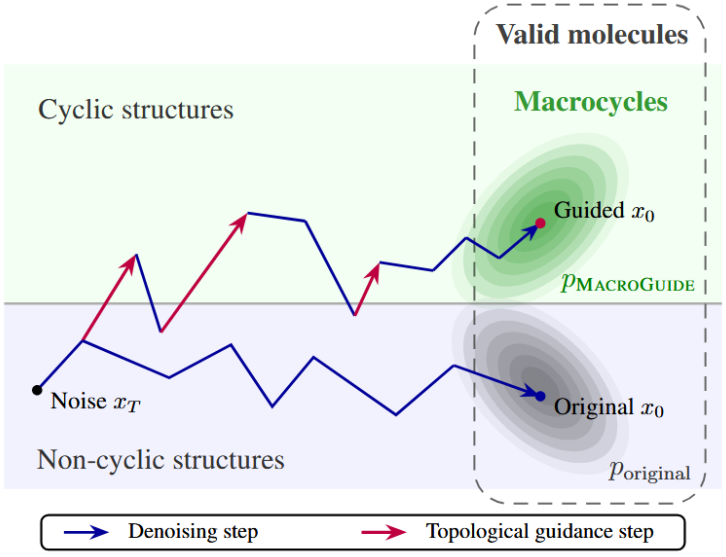
$$\hat{s}_\theta(x_t, t) \;=\; s_\theta(x_t, t) \;-\; \lambda_t \, \nabla_{x_t} F_{\mathrm{TDA}}(x_t)$$

training-free · *lightweight* · *flexible* · *general*

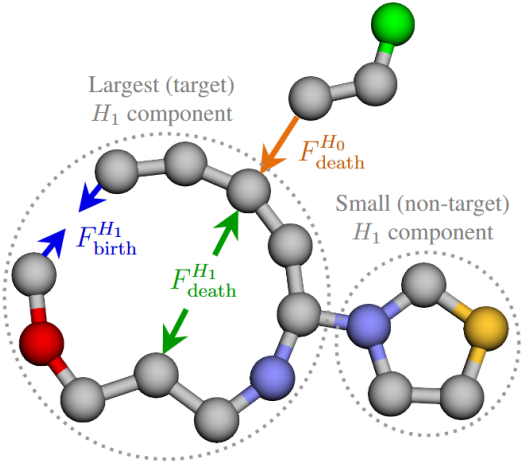
No retraining

Two objectives competing:

- Chemical validity
- F_{TDA}



TDA guidance



$F^{H_1}_{\text{death}}$

cycle size

$F^{H_1}_{\text{birth}}$

cycle closure

$F^{H_0}_{\text{death}}$

molecule connectivity

$$F_{\text{TDA}} = F^{H_1}_{\text{death}} + F^{H_1}_{\text{birth}} + F^{H_0}_{\text{death}}$$

Guidance terms

- **Cycle size** (H_1 death): push the death of the dominant H_1 feature into $[d_{\min}, d_{\max}]$

$$F^{H_1}_{\text{death}}(X) = \big(\mathrm{ReLU}(d_{\min} - d^*)\big)^2 + \big(\mathrm{ReLU}(d^* - d_{\max})\big)^2$$

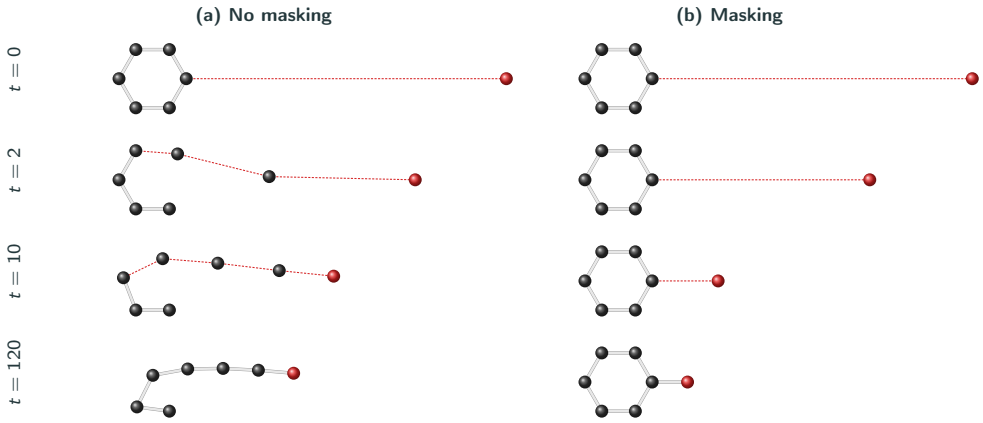
- **Cycle connectivity** (H_1 birth): closing edge below bond length $\ell^\star$

$$F^{H_1}_{\text{birth}}(X) = \mathrm{ReLU}(b^* - \ell^\star)$$

- **Molecule connectivity** (H_0 death): adjacent atoms distance below the typical bond length $\ell^\star$

$$F^{H_0}_{\text{death}}(X) = \sum_{j=1}^{N_0} \big(\mathrm{ReLU}(d_j - \ell^\star)\big)^2$$

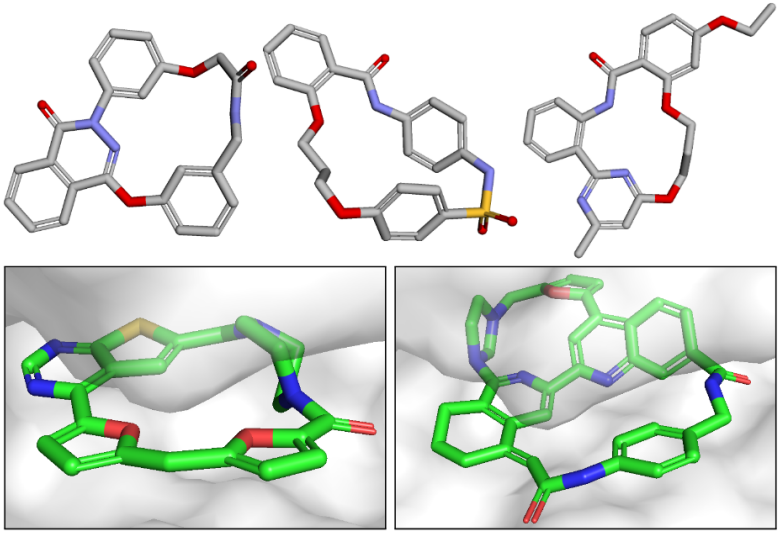
Gradient masking for H_0 stability



Problem: symmetric gradient drags the inner atom out of its cluster $\Rightarrow$ unzipping.

Fix: freeze the atom closer to the centroid: $m_u = 1\big(\|x_u - c\| \geq \|x_v - c\|\big)$.

Results: Generated macrocycles



Results

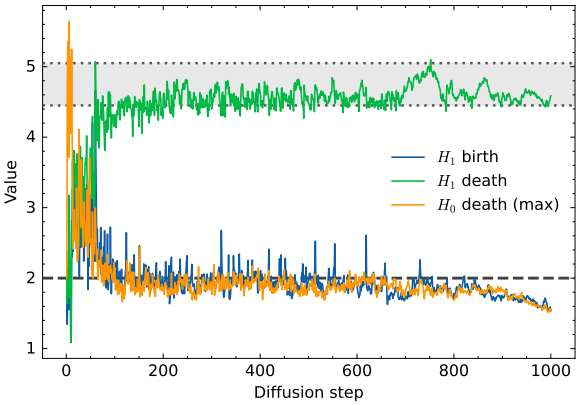
Unconditional (MolDiff)

- Macrocycles: 5.3% → **99.7%**
- PoseBusters: 66.3% → **80.5%**

Conditional (MolSnapper, protein pocket)

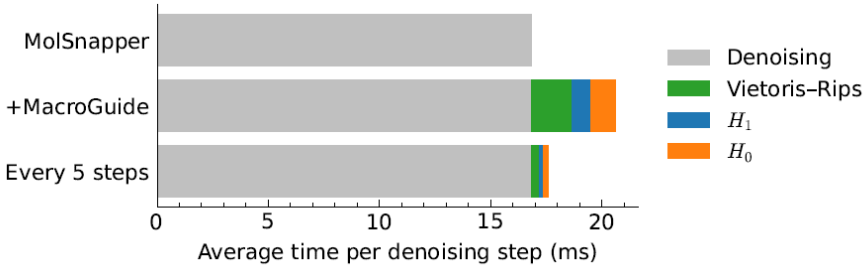
- Macrocycles: 0.3% → **99.5%**
- PoseBusters: 44.0% → **57.5%**

Convergence of topological features



- Topological features converge **fast** and reach a **stable region** of the macrocyclic space
- Chemical validity then has the **remaining denoising steps** to refine, mostly undisturbed

Is it fast? Yes.



References

[1] https://github.com/arneschneuing/DiffSBDD

[2] Munch, E. (2017). A user's guide to topological data analysis. Journal of Learning Analytics, 4(2), 47-61.

Thank you!

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