MuCO: Generative Peptide Cyclization

Empowered by Multi-stage Conformation Optimization

Yitian Wang

Gaoling School of Artificial Intelligence, Renmin University of China
DP Technology, Beijing

May 31, 2026

Table of Contents

Background: The Promise & The Bottleneck

- **High Therapeutic Potential**: Cyclic peptides offer enhanced stability, membrane permeability, and target-binding compared to linear peptides.
- **The Bottleneck**: Existing AI folding methods (e.g., GDL-base model, AlphaFold2-based model) are *deterministic*.
- **Core Issues**:
  - **Mode Collapse**: Fail to capture diverse conformational ensembles.
  - **Steric Clashes**: Struggle with dense macrocyclic geometric constraints.

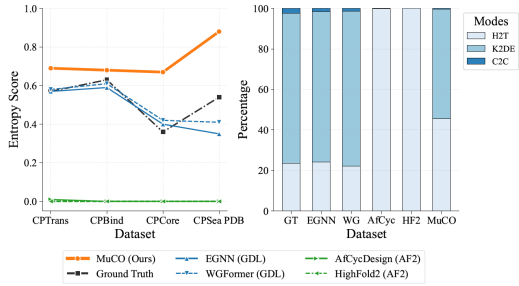
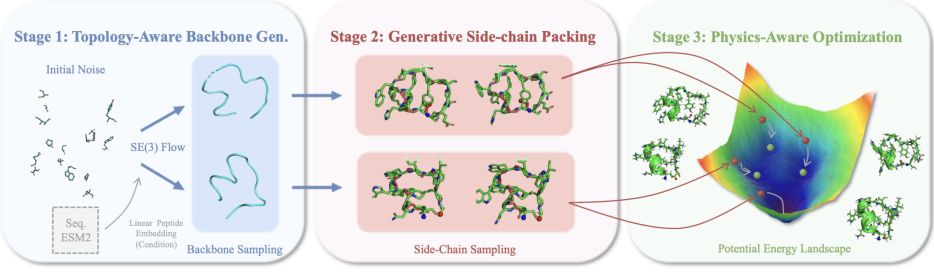


Figure: Structural Diversity and Mode Distribution Coverage on CPTrans.

MuCO: Multi-stage Conformation Optimization

Instead of end-to-end folding, MuCO decouples cyclization into 3 stages pipeline:

1. **Topology-Aware Backbone Generation**: SE(3) flow matching constructs closed ring scaffolds.
2. **Generative Side-chain Packing**: Torsional flow matching with *Cyclic RPE* to resolve dense steric clashes.
3. **Physics-Aware Optimization**: CHARMM36 forcefield relaxation to guarantee physical validity (energy minimization).



Efficient Exploration via Hierarchical Sampling

- **Tree-Structured Inference**: Sample K backbones $\times$ M side-chains in parallel.
- **Broad Potential Well Coverage**: Seeds massive conformational states, effectively exploring rugged energy landscapes.
- **Speed**: Amortized time is reduced to $\sim$ **41 ms/sample** (100x faster than AF2-based methods).

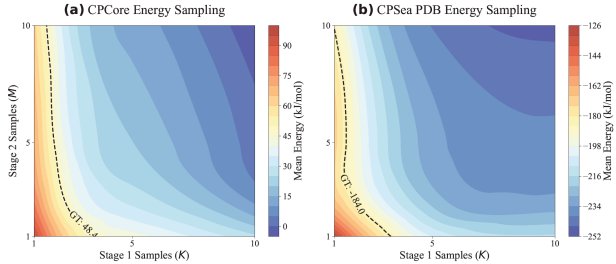


Figure: The heatmaps display the mean potential energy for a) CPCore and b) CPSea PDB with with Stage-1 and Stage-2 sample sizes.

Experimental Results: Breaking the Trade-off

- **Lower Energy**: Physically stable structures without unnatural strains.
- **Higher Diversity**: Successfully recovers all native cyclization modes (Head-to-Tail, Disulfide, Isopeptide).
- **Secondary Structure Recovery**: Generates native-like α-helices and β-sheets.

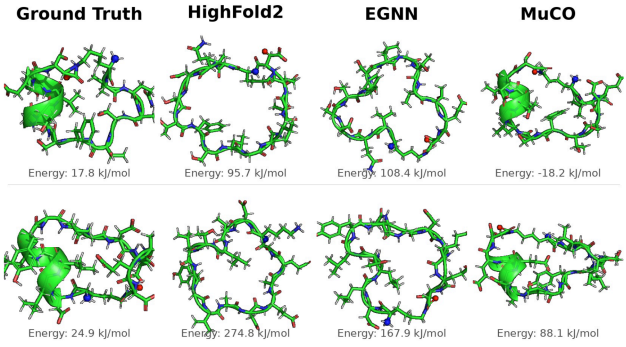


Figure: Case Study in CPSea PDB dataset.

Thanks for your listening!

Code and Data: `github.com/mianqiu00/MuCO`