SBProbMol^3: A Counterexample-Guided, Conditional Optimal-Transport Flow Matching for Structure-Based 3D Ligand Generation

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Generative modeling for structure-based drug design aims to generate three-dimensional ligands directly from the geometric and chemical context of protein binding pockets. However, existing methods still struggle to produce molecular configurations that are simultaneously geometrically coherent, chemically plausible, and physically valid. To address this challenge, we introduce SBProbMol^3, a novel generative methodology for pocket-conditioned 3D ligand generation with several key innovations. First, we design a counterexample-guided conditional entropic optimal transport coupling that uses hard-negative pocket-ligand pairs to steer the transport trajectory away from structurally unfavorable regions of conditional state space. Second, we develop a Geometric Heterogeneous Graph Attention Transformer as a geometry-aware backbone for the generative model, allowing the learned transport dynamics to capture better long-range 3D context while preserving heterogeneous relational structure and equivariant symmetry. Third, we formulate a multi-modal flow matching objective on a joint Euclidean-simplex-torus-SO(3) manifold, allowing coordinates, categorical variables, torsional angles, and residue orientations to evolve according to their intrinsic geometry. The finalized framework is evaluated on a leakage-controlled benchmark constructed from SAIR and PLINDER protein-ligand datasets. Experimental results show that our proposed framework achieves superior performance in structural validity and binding quality, while maintaining essential molecular properties and sample diversity at levels competitive with other baselines. SBProbMol^3 establishes a foundational framework for not only structure-based drug design but also generative modeling on hybrid geometric state space.

Awards Won:
Association for the Advancement of Artificial Intelligence: Honorable Mention (do not read aloud). Winners receive a student level membership. Information is included separately in the SAO Portal.