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DiffDesign – An SE(3)-Equivariant Diffusion Model for Molecule Linker Generation

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Recent advances in targeted drug design have demonstrated that incorporating 3D structural information yields superior performance compared to target-free models, as this approach enables explicit modeling of atomic interactions in three-dimensional space. Generative models have achieved remarkable success in drug discovery, particularly in fragment-based drug design applications, such as scaffold hopping and proteolysis-targeting chimera (PROTAC) design.

In this work, we present DiffDesign, an SE(3)-equivariant three-dimensional conditional diffusion model designed to address the molecular linker design problem. Given a specific protein pocket, our model generates the missing atoms required to connect two disconnected molecular fragments physically. On standard benchmarks, DiffDesign surpasses existing methods, yielding molecules with greater diversity and improved synthetic accessibility. Our model achieves a uniqueness rate comparable to DiffLinker while producing 5% more RDKit-valid molecules and 26.8% more novel molecules, indicating more effective exploration of novel yet valid chemical space.

Empirical studies validate that our approach achieves state-of-the-art performance in terms of synthetic accessibility and drug-likeness, highlighting its practical utility in drug design pipelines.