# PILOTING STRUCTURE-BASED DRUG DESIGN VIA MODALITY-SPECIFIC OPTIMAL SCHEDULE

**Keyue Qiu**[1,2*] **Yuxuan Song**[1,2*] **Zhehuan Fan**[3] **Peidong Liu**[4] **Zhe Zhang**[2]
**Mingyue Zheng**[3] **Hao Zhou**[1†] & **Wei-Ying Ma**[1]
[1] Institute for AI Industry Research (AIR), Tsinghua University
[2] Department of Computer Science and Technology, Tsinghua University
[3] Shanghai Institute of Materia Medica, Chinese Academy of Sciences
[4] Sichuan University
qky22@mails.tsinghua.edu.cn, {zhouhao,maweiying}@air.tsinghua.edu.cn

## ABSTRACT

Structure-Based Drug Design (SBDD) is crucial for identifying bioactive molecules. Recent deep generative models are faced with challenges in geometric structure modeling. A major bottleneck lies in the twisted probability path of multi-modalities—continuous 3D positions and discrete 2D topologies—which jointly determine molecular geometries. By establishing the fact that noise schedules decide the Variational Lower Bound (VLB) for the twisted probability path, we propose VLB-Optimal Scheduling (VOS) strategy in this under-explored area, which optimizes VLB as a path integral for SBDD. Our model effectively enhances molecular geometries and interaction modeling, achieving state-of-the-art PoseBusters passing rate of 95.9% on CrossDock, more than 10% improvement upon strong baselines, while unlocking the potential of repurposing SBDD model as docking method without retraining, with 44.0% RMSD $<$ 2Å on PoseBusters V2.

*Equal contribution. Correspondence to Hao Zhou (zhouhao@air.tsinghua.edu.cn).