3DMolFormer: A Dual-channel Framework for Structure-based Drug Discovery

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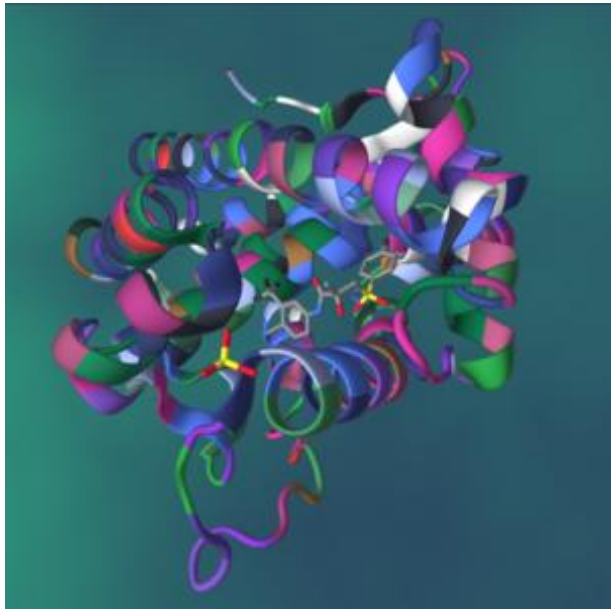
Presenter: Xiuyuan Hu, Tsinghua University

Co-authors: Guoqing Liu, Can (Sam) Chen, Yang Zhao, Hao Zhang, Xue Liu

Structure-based Drug Discovery

- Structure-based Drug Discovery (SBDD) is one of the most critical strategies in drug discovery practices, focusing on the structure and interactions of protein-ligand complexes.

- Two core SBDD tasks:
  - Protein-ligand binding pose prediction (docking)
  - Pocket-aware 3D drug design

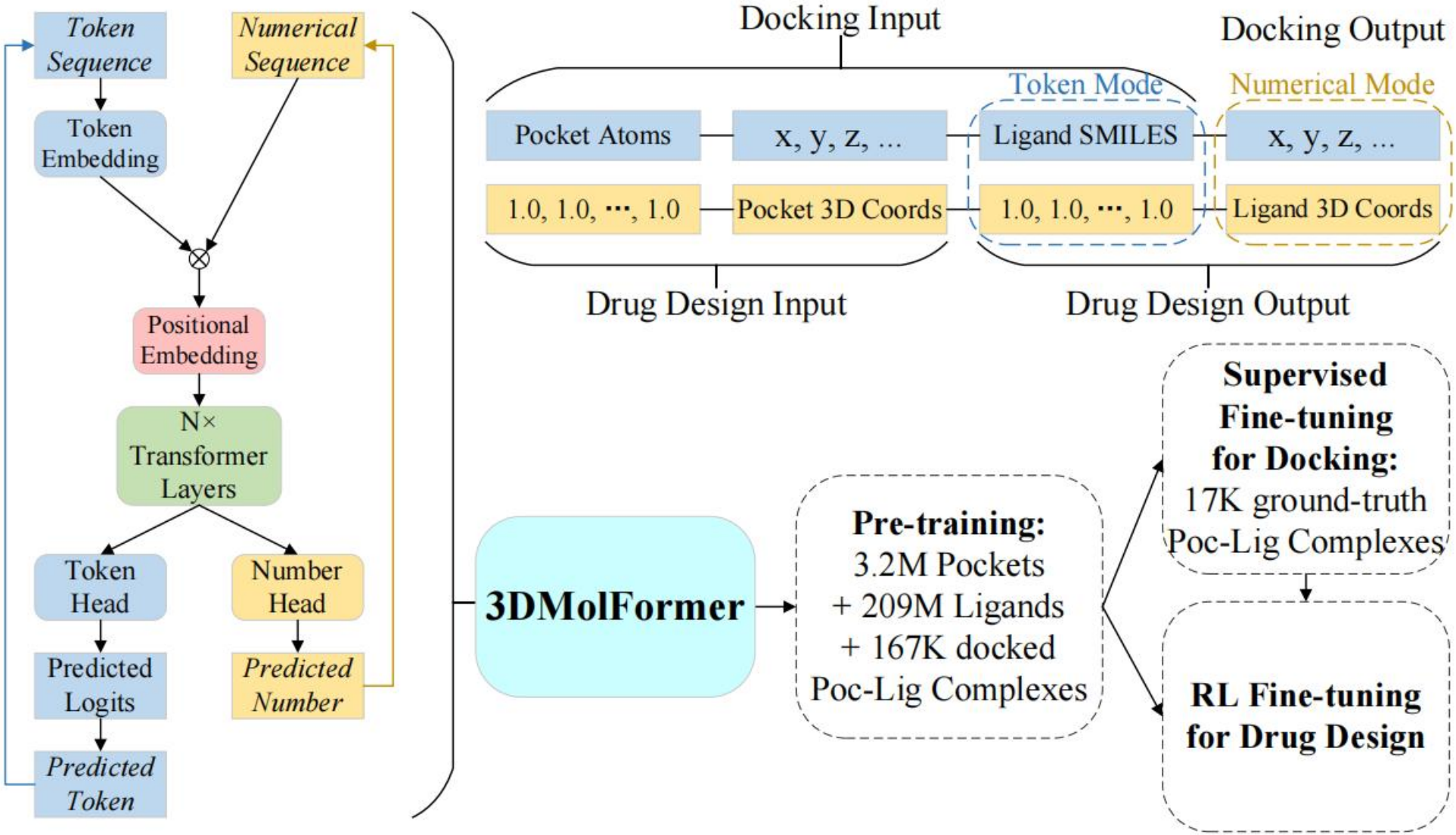


A Protein-ligand complex (from Wikipedia)

Three limitations of existing SBDD methods

- **Underutilized duality**: Protein-ligand docking and pocket-aware 3D drug design are naturally dual tasks, and improvements in docking performance could directly benefit drug design. However, this duality has not been leveraged by previous machine learning approaches.
- **Challenges in modeling 3D information**: Modeling 3D information is a key difficulty in SBDD, as protein sequences and small molecule graphs contain only discrete information, whereas 3D coordinates are continuous values.
- **Limited data**: Ground-truth data on protein-ligand complexes are scarce. Currently, the largest dataset, PDBbind, contains fewer than 20,000 complexes, which is insufficient for training a robust machine learning model.

Our methodology: 3DMolFormer



3DMolFormer - Parallel Sequence Format for Protein-ligand Complexes

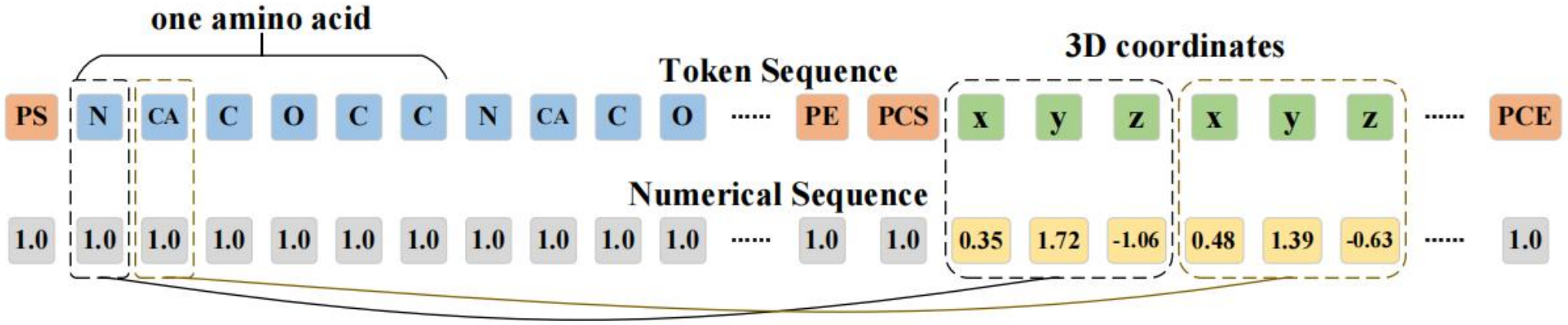


Figure 1: The parallel sequence of a protein pocket with 3D coordinates.

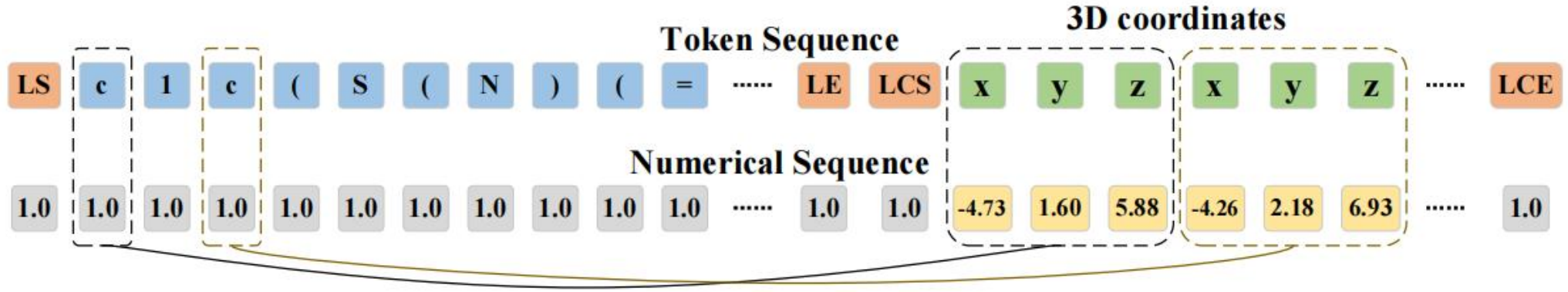
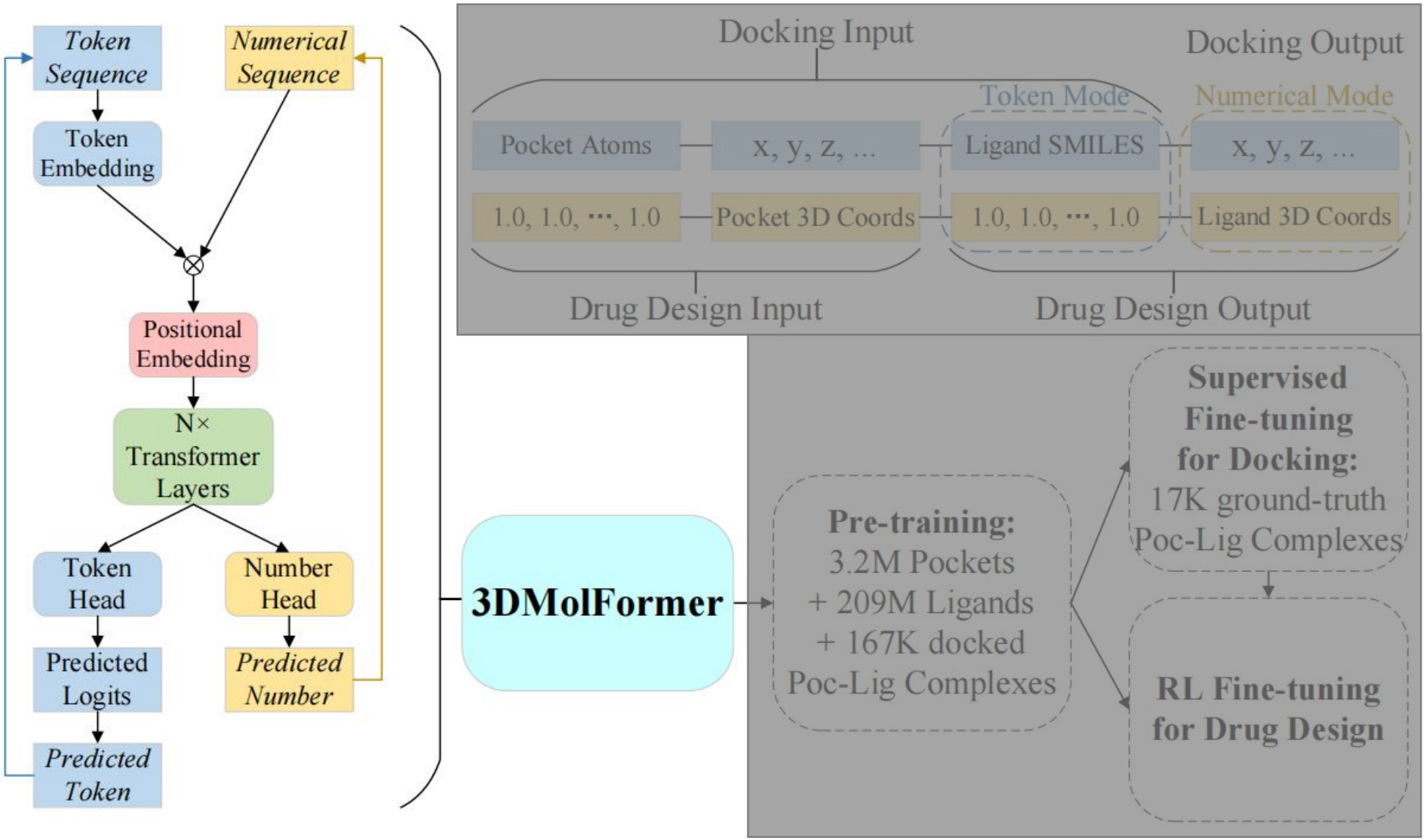
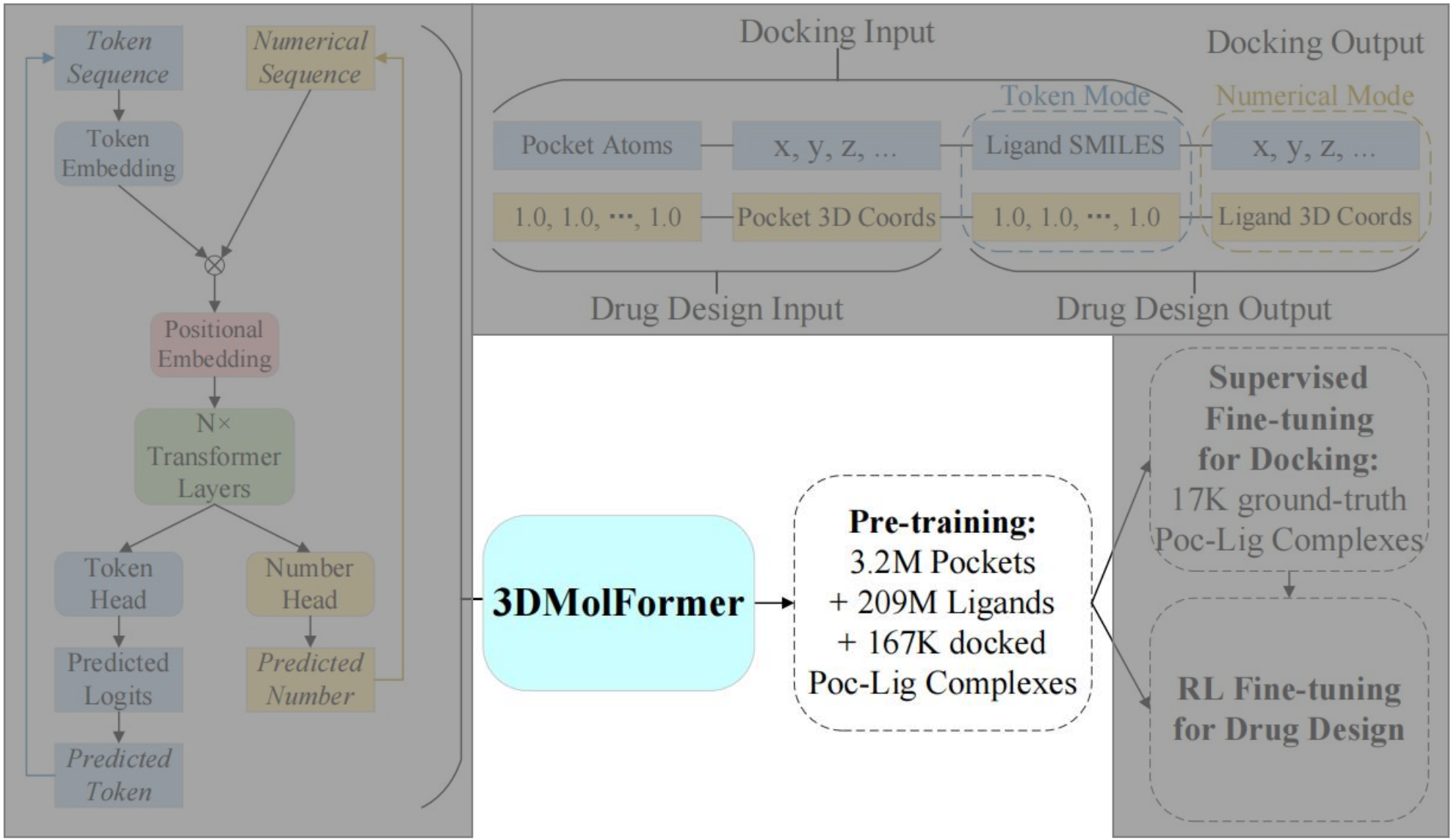


Figure 2: The parallel sequence of a small molecule ligand with 3D coordinates.

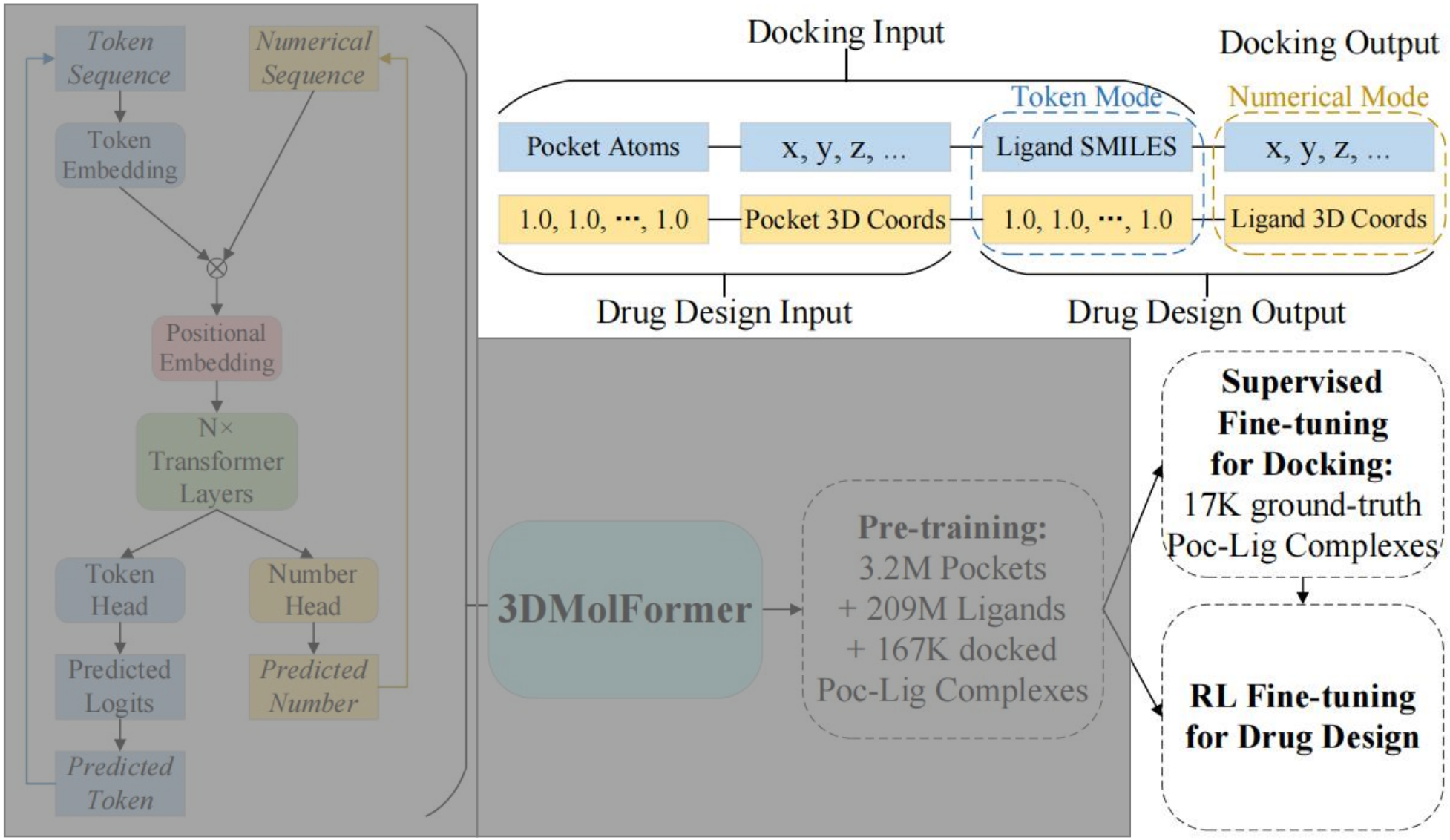
3DMolFormer - Dual-channel Model Architecture



3DMolFormer - Large-scale Pre-training



3DMolFormer - Fine-tuning for Two Tasks



Experiments - Docking

Table 1: Experimental results of 3DMolFormer, its variants, and other baselines on protein-ligand binding pose prediction, following the results reported in Uni-Mol (Zhou et al., 2023a). (↑) / (↓) denotes that a higher / lower value is better. The best result in each column is **bolded**.

Methods	%<1.0Å (↑)	%<2.0Å (↑)	%<3.0Å (↑)	%<5.0Å (↑)	Avg. (↓)
AutoDock4	21.8	35.4	47.0	64.6	3.53
AutoDock Vina	44.2	64.6	73.7	84.6	2.37
Vinardo	41.8	62.8	69.8	76.8	2.49
Smina	**47.4**	65.3	74.4	82.1	1.84
Uni-Mol	43.2	80.4	87.0	94.0	1.62
3DMolFormer w/o PT	15.5	57.8	78.1	92.4	2.25
3DMolFormer w/o DA	10.3	51.0	74.9	91.6	2.45
3DMolFormer	43.8	**84.9**	**96.4**	**98.8**	**1.29**

Experiments - Pocket-aware 3D Drug Design

Table 2: Experimental results of 3DMolFormer and other baselines on pocket-aware 3D drug design, following the results reported in DecompDiff (Guan et al., 2023b). (↑) / (↓) denotes that a higher / lower value is better. The best result in each column is **bolded**.

Methods	Vina Score (↓)	Vina Dock (↓)	QED (↑)	SA (↑)	Success Rate (↑)
Reference	-6.36	-7.45	0.48	0.73	25.0%
AR	-5.75	-6.75	0.51	0.63	7.1%
liGAN	-	-6.33	0.39	0.59	3.9%
GraphBP	-	-4.80	0.43	0.49	0.1%
Pocket2Mol	-5.14	-7.15	**0.56**	0.74	24.4%
TargetDiff	-5.47	-7.80	0.48	0.58	10.5%
DecompDiff	-5.67	-8.39	0.45	0.61	24.5%
3DMolFormer	**-6.02**	**-9.48**	0.49	**0.78**	**85.3%**

Future Directions

- SE(3)-equivariant architectures vs. Non-equivariant ones
  - Scaling of data / model

- Incorporation of protein flexibility
- Explicit modeling of intermolecular interactions
- Extension to all-atom modeling of proteins