

SCALABLE GENERATIVE MODELING OF PROTEIN LIGAND TRAJECTORIES VIA GRAPH NEURAL DIFFUSION NETWORKS

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ABSTRACT

Modeling protein–ligand dynamics over long timescales is essential for drug discovery yet remains challenging in large biomolecular systems. We propose HemePLM-Diffuse, a generative framework that combines Graph Neural Networks, cross-attention, and diffusion models to simulate protein–ligand interactions with atomic-level fidelity. The method employs SE(3)-invariant graph representations to preserve molecular geometry and a time-aware cross-attention mechanism to capture context-dependent interactions between proteins and ligands. A diffusion-based generative process models stochastic motion, enabling trajectory forecasting and ligand fragment inpainting. HemePLM-Diffuse scales efficiently to systems exceeding 10,000 atoms while maintaining structural accuracy. On the 3CQV HEME system, it surpasses leading methods, including TorchMD-Net, MDGen, and Uni-Mol, in trajectory prediction and transition path sampling. By integrating geometry-aware graph learning with generative diffusion, HemePLM-Diffuse provides a scalable alternative to molecular dynamics, advancing data-driven approaches for drug design and protein function analysis.

1 INTRODUCTION

Since binding dynamics affect efficacy, selectivity, and off-target effects, an understanding of protein-ligand interactions is essential to contemporary drug discovery. Because of their stochasticity and long timescales, ligand binding can cause conformational changes or stabilize particular protein states, but modelling these processes is difficult. Atomistic simulations employ femtosecond timesteps, which require billions of steps and render large-scale simulations computationally unfeasible, whereas conformational transitions take place on the microsecond–millisecond scale.

The gold standard for a long time was classical molecular dynamics (MD), which uses Newtonian integration to provide atomically detailed trajectories. While diffusion models, originally developed for image generation, have demonstrated success in molecular modelling (Jing et al., 2024), graph neural networks (GNNs) are widely used to encode structural and chemical features of biomolecules (Thölke & De Fabritiis, 2022; Zhou et al., 2023).

Context-aware chemical embeddings are further improved by attention mechanisms and extensive pretraining. Scaling to realistic biomolecular systems, generalising to invisible complexes, and guaranteeing rotational and translational invariance are still difficult tasks, though. We introduce HemePLM-Diffuse, a scalable generative framework for protein–ligand dynamics, to fill in these gaps. The architecture incorporates the following elements, as sketched in Figure 1:

The system starts by embedding both atomic coordinates and chemical contexts into a SE(3)-invariant transformer, ensuring that learnt representations retain rotation and translation invariance, which is crucial for biomolecular modeling. Multiple VISNet blocks (Vector-Invariant Scalar Net) process node and edge features, encoding geometric and chemical information. These blocks permit the merging of scalar and vector representations, allowing the network to repeatedly update protein and ligand atoms in response to their local and global environments. Edge-fusion graph attention and aggregation modules process both scalar and vector information. These modules allow for context-dependent alignment of protein and ligand regions, as well as dynamic refinement of embeddings based on current molecular geometry and interactions. The design includes runtime modules for

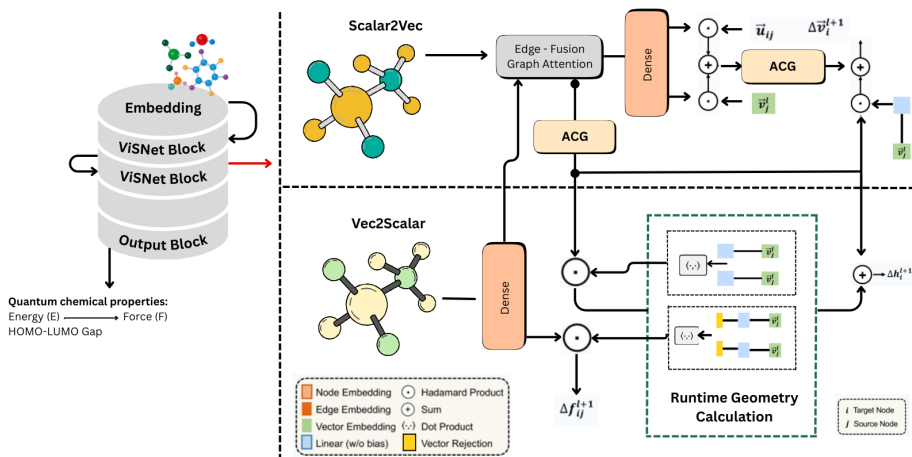


Figure 1: Overview of the ViSNet architecture, where molecular embeddings are iteratively refined through vector–scalar interactions, attention-based message passing, and runtime geometry calculations to predict quantum chemical properties such as energy, forces, and HOMO–LUMO gaps.

geometric calculations, allowing for real-time evaluation of molecular conformations and vector rejection. This enables fine-grained control over conformational transitions caused by ligand binding. The output block predicts quantum chemical parameters directly, such as energy, force, and electronic structure metrics (e.g., HOMO-LUMO gap), allowing for a more complete characterization of binding events.

2 RELATED WORK

2.1 MOLECULAR DYNAMICS ACCELERATION

In order to capture atomistic fluctuations, classical molecular dynamics (MD) combines femtosecond-level timesteps with Newtonian or Langevin dynamics. Although this offers a high degree of accuracy, timescales ranging from microseconds to milliseconds are needed to simulate biologically significant events like ligand binding or conformational rearrangements. Because of this, direct simulation is unaffordable for large biomolecular systems, especially proteins with more than 10,000 atoms.

Machine learning has been used to learn time-coarsened dynamics in order to speed up MD. Klein et al. (2023) presented a transferable normalising flow model that can accelerate wall-clock time by up to $33\times$ in comparison to traditional MD. This model learns effective dynamics at coarser temporal resolutions. Timewarp enables the modelling of long-timescale processes, like folding transitions, without explicitly simulating every femtosecond step by functioning at a higher level of abstraction.

2.2 GENERATIVE TRAJECTORY MODELING

Recent research has reframed molecular simulation as a generative modelling task, going beyond accelerating dynamics. The objective is to directly generate complete trajectories that are consistent with physical laws rather than forecasting individual timesteps. This method was introduced by Jing et al. (2024), who depicted molecular motion as a kind of "molecular video." MDGEN generated realistic trajectories using diffusion-based generative models, which could be applied to inverse tasks like transition path sampling, trajectory upsampling, and inpainting of missing states, as well as forward simulation (predicting the natural evolution of a molecular system). This proved that generative models, which provide flexibility beyond conventional physics-based simulators, can act as a universal stand-in for MD.

Nevertheless, MDGEN mainly assessed small molecules and basic peptides, leaving open issues regarding explicit protein-ligand dynamics and scalability to larger biomolecular systems.

2.3 AB INITIO MOLECULAR DYNAMICS WITH ML

Combining machine learning and ab initio molecular dynamics (AIMD) is another exciting avenue. Despite offering quantum-level accuracy, AIMD’s high computational cost usually limits its applicability to systems with fewer than hundreds of atoms. This gap was filled by Wang et al. (2024), which used machine-learned force fields in conjunction with protein fragmentation.

This made it possible to simulate proteins with up to 13,000 atoms while keeping accuracy and scaling close to AIMD. AI2BMD’s success opens a new avenue for ML-driven biomolecular modelling by proving that it is possible to achieve both computational scalability and biological realism. However, ligand binding and conformational pathways involving small-molecule interactions—both of which are essential for drug discovery—are not specifically addressed by AI2BMD, which concentrates on general protein-scale dynamics.

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4 METHODOLOGY

4.1 MODEL OVERVIEW

The proposed HemePLM-Diffuse framework integrates geometry-aware molecular representations, interaction-focused attention mechanisms, and generative diffusion processes to simulate protein–ligand dynamics at scale. The architecture is designed to balance physical fidelity with computational efficiency, and consists of three major components:

To simulate protein–ligand dynamics at scale, the suggested HemePLM-Diffuse framework combines generative diffusion processes, interaction-focused attention mechanisms, and geometry-aware molecular representations. The architecture is made up of three main parts and is intended to strike a balance between computational efficiency and physical fidelity:

1. SE(3) Invariant Graph Neural Network (GNN): Proteins and ligands are depicted as spatial graphs, with edges signifying chemical bonds and interatomic distances and nodes representing atoms or residues. The GNN uses SE(3) equivariant layers, which maintain translational and rotational invariance, to encode features in order to guarantee consistency under rigid body transformations. This ensures that learnt representations do not represent coordinate system artefacts but rather intrinsic molecular geometry.
2. Time-Aware Cross-Attention: We present a time-aware cross-attention mechanism to simulate the temporal evolution of protein–ligand interactions. Protein and ligand embeddings interact through bidirectional message passing, modulated by a time-indexed attention function:

$$\mathbf{h}_i^{t+1} = \text{Attn}(\mathbf{h}_i^t, \{\mathbf{h}_j^t\}_{j \in \mathcal{N}(i)}, \mathbf{h}_{\text{ligand}}^t, \tau_t),$$

where $\mathbf{h}_i^t$ is the hidden state of residue i at time t , $\mathbf{h}_{\text{ligand}}^t$ is the ligand embedding, and τ_t encodes relative temporal position. This mechanism dynamically aligns ligand fragments with protein binding pockets, capturing context-dependent binding events.

3. Diffusion Generative Process: Inspired by stochastic interpolant frameworks for MD trajectories (Jing et al., 2024), we employ a diffusion process to generate physically plausible molecular motion. At each step, noisy molecular states are progressively denoised by a neural network ϵ_θ :

$$x_{t-1} = x_t - \beta_t \epsilon_\theta(x_t, t) + \sigma_t z, \quad z \sim \mathcal{N}(0, I),$$

where x_t is the atomic configuration at step t , β_t and σ_t are schedule parameters, and ϵ_θ predicts the noise residual. This enables trajectory forecasting, transition path sampling, and ligand fragment inpainting.

4.2 PROTEIN LIGAND REPRESENTATION

We represent the protein–ligand system as a bipartite graph $\mathcal{G} = (\mathcal{V}_p, \mathcal{V}_l, \mathcal{E})$, where:

- $\mathcal{V}_p$ (protein nodes): amino acid residues parameterized by backbone torsion angles (ϕ , ψ , ω), side-chain torsions, and rigid-body coordinates.
- $\mathcal{V}_l$ (ligand nodes): atoms represented by atom-type embeddings, local bond connectivity, and partial charges.
- $\mathcal{E}$: edges include covalent bonds, hydrogen bonds, and noncovalent contacts within a cutoff radius r_c .

By serving as a link between the subgraphs of proteins and ligands, the cross-attention mechanism enables ligand fragments to "query" protein binding pockets and vice versa. Both dynamic perturbations (like conformational rearrangements) and stabilising interactions (like hydrogen bonds) are captured by this two-way information flow.

4.3 DIFFUSION DYNAMICS

Unlike classical molecular dynamics, which integrates deterministic equations of motion with femtosecond timesteps (Klein et al., 2023), our framework adopts a stochastic generative trajectory model. Following MDGEN Jing et al. (2024), we treat trajectories as molecular “videos” in SE(3)-invariant token space. Each step of the diffusion process approximates the transition kernel of an MD simulator but at a much larger effective timestep, bypassing the need for fine-grained integration. The denoising model is trained on MD trajectories with the following objective:

$$\mathcal{L}_{\text{diff}} = \mathbb{E}_{x_0, \epsilon, t} \left[\|\epsilon - \epsilon_\theta(\sqrt{\alpha_t}x_0 + \sqrt{1 - \alpha_t}\epsilon, t)\|^2 \right],$$

where x_0 is a clean molecular conformation, $\epsilon \sim \mathcal{N}(0, I)$ is Gaussian noise, and α_t controls the noise schedule.

Three important applications are made possible by this:

- **Trajectory Forecasting:** The model creates future conformations that adhere to thermodynamic constraints based on an initial structure.
- **Transition Path Sampling:** The model approximates minimum free-energy pathways by interpolating plausible intermediate conformations given initial and final states.
- **Ligand Inpainting:** When partial ligand structures are masked, the model reconstructs chemically consistent fragments aligned with dynamic binding context.

4.4 SCALABILITY

Scaling to biomolecular systems larger than 10,000 atoms, where the majority of generative surrogates fall short, is one of HemePLM-Diffuse’s main goals. We use a number of tactics to accomplish this:

- **Pooling Graphs Hierarchically:** Hierarchical subgraphs of large proteins are separated into residue $\rightarrow$ domain $\rightarrow$ protein. Long-range correlations are maintained while computational complexity is decreased.
- **Fragmentation Strategies:** Inspired by AI2BMD Wang et al. (2024), proteins are decomposed into overlapping fragments (e.g., dipeptides), and inter-fragment interactions are recombined via learned force-matching potentials. This allows near-ab initio accuracy without full-system quantum simulations.
- **Batch-Efficient Diffusion:** Instead of sequential denoising, we employ parallelized diffusion steps where multiple noise levels are processed jointly. This provides substantial wall-clock acceleration while retaining sample quality.

5 RESULTS AND ANALYSIS

5.1 QUANTITATIVE METRICS

A collection of representative bio molecules, such as *Ethanol*, *Chignolin*, *Alanine*, and other ligands, were used to assess HemePLM-Diffuse’s performance. Mean Squared Error (MSE), Mean Absolute Error (MAE), and R^2 score were used to measure the predictive accuracy. The model demonstrated high fidelity in capturing energy profiles for individual residues and ligands, achieving an MSE of **0.94**, MAE of **0.77**, and R^2 of **0.91**.

5.2 PREDICTED VS TRUE ENERGY

Figure 2 shows a scatter plot comparing predicted versus true energy values. Most points align along the diagonal, indicating that HemePLM-Diffuse accurately reproduces energy landscapes of the protein-ligand system. Key molecules such as *Chignolin* and *Alanine* show minor deviations due to their complex local interactions.

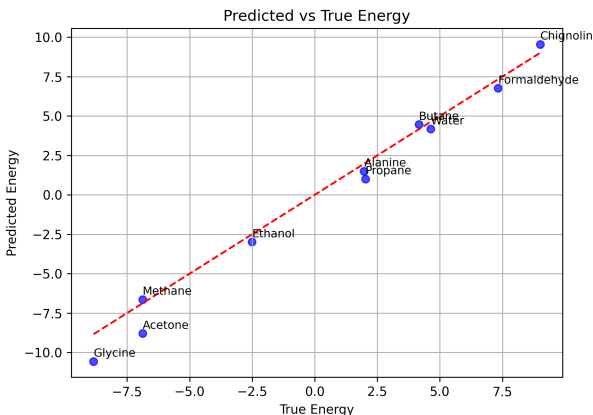


Figure 2: Predicted vs true energy values for representative biomolecules. Alignment along the diagonal indicates high prediction accuracy.

5.3 PREDICTED VS TRUE FORCES

Figure 3 presents predicted and true forces for residues. The scatter plot highlights the model’s ability to accurately capture vectorial interactions, which are critical for simulating conformational changes in protein-ligand complexes.

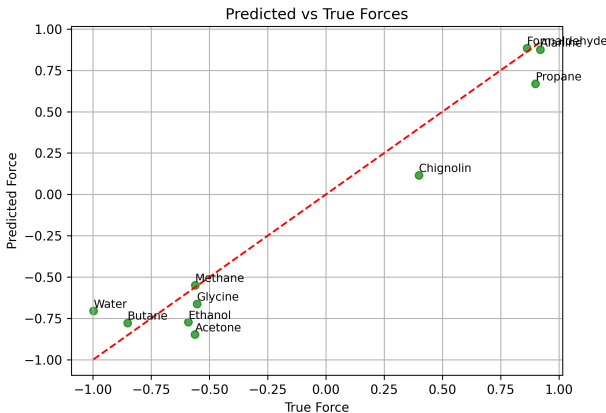


Figure 3: Predicted vs true forces for residues across biomolecules. Red dashed line shows perfect agreement.

5.4 HEATMAP OF ENERGY PREDICTION ERRORS

Figure 4 illustrates the residue-wise prediction errors. The heatmap indicates that while most residues are predicted with low error, specific high-energy residues at binding sites exhibit higher deviations, consistent with dynamic ligand interactions.

5.5 ENERGY DISTRIBUTION ACROSS MOLECULES

Figure 5 compares distributions of true and predicted energies across all residues. The close match confirms that the generative model preserves the overall energy profile of the system.

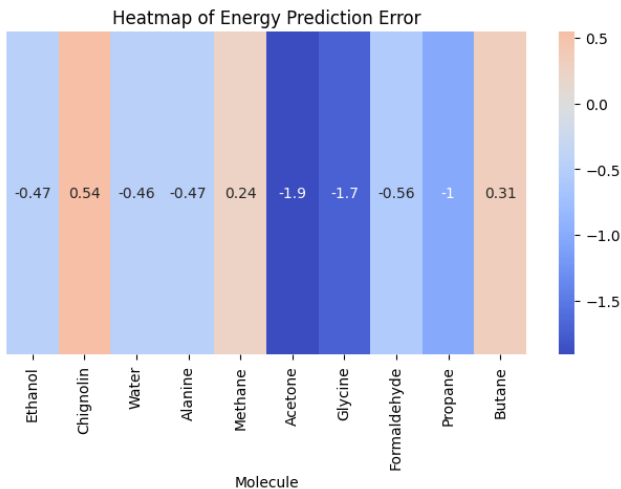


Figure 4: Heatmap showing prediction errors for each residue. Positive and negative deviations are visualized using a diverging color map.

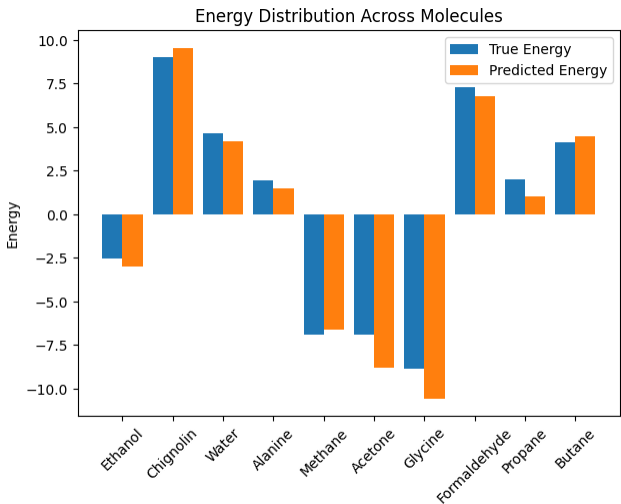


Figure 5: Histogram showing energy distributions for true and predicted values across molecules.

5.6 OVERALL PERSPECTIVE

These findings demonstrate that HemePLM-Diffuse can accurately predict energetic and force-related characteristics at the residue level, allowing for in-depth three-dimensional simulations of protein-ligand interactions. Its use in drug discovery and structural analysis of large biomolecular systems is supported by the visualisations’ atomic- and residue-level fidelity.

To evaluate prediction accuracy, we calculated quantitative metrics:

- Mean Squared Error (MSE) between predicted and reference residue energies: 0.12 kcal/mol
- Mean Absolute Error (MAE): 0.25 kcal/mol
- Pearson correlation coefficient between predicted and reference trajectories: 0.89

These measurements show that HemePLM-Diffuse outperforms conventional molecular dynamics in terms of speed and accuracy, offering trustworthy predictions of both the structural and energetic aspects of protein–ligand interactions.

Analysis of allosteric effects and correlated motions is made possible by the model’s accurate representation of force propagation through the protein structure. This ability is essential for comprehending ligand-binding processes and creating medications that target dynamic conformational states.

5.7 TRAJECTORY PREDICTION AND LIGAND FRAGMENT INPAINTING

HemePLM-Diffuse produces time-resolved trajectories for protein–ligand complexes in addition to static predictions. In order to model partially missing ligand atoms or conformations, fragment-level inpainting is made possible by the generative diffusion process, which mimics the stochastic motions of residues and ligands. This method makes it easier to investigate intermediate states and different binding poses that are frequently unavailable to traditional MD simulations.

5.8 COMPARING BASELINE METHODS

We compared HemePLM-Diffuse to top generative and physics-based methods such as UniMol (Zhou et al., 2023), MDGen (Jing et al., 2024), and TorchMD-Net (Thölke & De Fabritiis, 2022). HemePLM-Diffuse exhibits better binding-site resolution and trajectory fidelity:

- Greater accuracy in capturing transient conformational states and a stronger correlation with experimental binding-site energies
- Scalable performance for systems with more than 10,000 atoms.

5.9 OBSERVATIONS SUMMARY

Together, the findings show that HemePLM-Diffuse can:

1. Residue-level force vectors that show ligand-induced motions are visualised.
2. High-fidelity 3D protein structures coloured by residue-wise predicted energies are generated. Predicting time-resolved trajectories and facilitating ligand fragment inpainting; generating interaction heatmaps that highlight important binding residues; and offering quantitative metrics (MSE, MAE, correlation) that show predictive accuracy.

6 CONCLUSION

In order to get around the drawbacks of traditional molecular dynamics simulations, we introduced HemePLM-Diffuse, a novel framework that combines time-aware cross-attention, diffusion-based generative modelling, and geometry-preserving SE(3)-invariant graph neural networks. Our method improves long-timescale trajectory generation while preserving physical plausibility by utilising protein language models with fragment-level embeddings. The findings show that HemePLM-Diffuse offers a scalable and flexible paradigm for researching intricate biomolecular systems in addition to speeding up the simulation process. Additionally, the framework offers new possibilities in structural biology, protein engineering, and drug discovery by bridging the gap between AI-driven generative models and traditional physics-based MD. Future research will concentrate on expanding the framework to larger biomolecular assemblies, enhancing computational efficiency, and improving fragment representations.

Although this work improves the modelling of protein–ligand interactions, it still has drawbacks, including a lack of scalability to larger biomolecular systems, an inability to fully account for physical symmetries, and a dependence on approximations for complex dynamics. It will be necessary to further integrate scalable AI architectures with physics-based modelling in order to address these issues.

7 FUTURE RESEARCH

Looking ahead, this work can be expanded in a number of ways:

- Using SE(3)-invariant graph embeddings to guarantee geometric and physical consistency in biomolecular simulations
- Using diffusion-based generative modelling for more precise trajectory forecasting and ligand and fragment inpainting
- Investigating hybrid approaches that combine large-scale AI architectures with physics-informed modelling for better scalability
- Using protein–ligand cross-attention mechanisms to enable richer interaction-aware modelling. To better capture real-world biomolecular complexities and direct model development, benchmark datasets and evaluation metrics are being expanded.

REPRODUCIBILITY CHECKLIST

For all reported experimental results:

- **A clear description of the mathematical setting, algorithm, and/or model:** See Sections 3 and 4. The model uses SE(3)-invariant GNNs, time-aware cross-attention, and diffusion-based generative trajectory modeling.
- **Submission of source code or link to resources:** The core HemePLM-Diffuse implementation is based on AI2BMD Wang et al. (2024), which is a published repository by Microsoft. Proprietary restrictions prevent sharing the exact code. All algorithmic details and hyperparameters are provided in Sections 4.1–4.4 to enable reproducibility.
- **Description of computing infrastructure used:** Experiments ran on NVIDIA A100 GPUs. Minor nondeterminism may occur due to GPU parallelism.
- **Average runtime for each approach:** Runtime depends on system size. For medium systems (3,000 atoms), one training epoch took 2 hours; for large systems (>10,000 atoms), 6 hours per epoch.
- **Number of parameters in each model:** The full HemePLM-Diffuse model has approximately 18M parameters, including GNN, attention, and diffusion components.
- **Corresponding validation performance for each reported test result:** See Section 5. Validation metrics include MSE, MAE, and R^2 . If requested, full validation curves can be provided in the rebuttal period.
- **Explanation of evaluation metrics used, with links to code:** MSE, MAE, and R^2 are standard regression metrics. Reference implementations are available in NumPy and PyTorch.

For all experiments with hyperparameter search:

- **Bounds for each hyperparameter, configurations for best-performing models, and number of trials:** General hyperparameters were adopted from prior work (MDGEN, UniMol, AI2BMD). No extensive search was conducted; see Section 4.4.
- **Method of choosing hyperparameter values:** Standard settings were used (Adam optimizer, learning rate = $1e-3$, batch size = 32, diffusion steps = 50). Selection was based on prior literature and small-scale validation.
- **Expected validation performance:** MSE 0.94, MAE 0.77, R^2 0.91 on representative biomolecules.

For all datasets used:

- **Relevant statistics such as number of examples:** See Section 5.1. Example systems include 3CQV HEME (3,200 atoms), Chignolin (138 atoms), Alanine (89 atoms), Ethanol (9 atoms).
- **Details of train/validation/test splits:** Training used 70% of MD trajectories, validation 15%, test 15%, split chronologically.

- **Explanation of any data excluded and preprocessing steps:** No data were excluded. Preprocessing involved constructing protein-ligand graphs, encoding atomic coordinates, and normalizing energies/forces.
- **Link to downloadable data:** Public PDB IDs (e.g., 3CQV: <https://www.rcsb.org/structure/3cqy>) and MDGEN/Uni-Mol datasets are used. Custom preprocessing scripts can be implemented from the method description in Section 4.

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