HOW TO GO WITH THE FLOW: AN ANALYSIS OF FLOW MATCHING MOLECULAR DOCKING PERFORMANCE WITH PRIORS OF VARYING INFORMATION CONTENT

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ABSTRACT

Predicting molecular docking poses with flow matching algorithms represents both a promising opportunity and a challenging task. Recently, a flow matching algorithm, HarmonicFlow, has been reported to yield encouraging molecular docking results. The method employs a harmonic prior to make initial predictions. In light of the importance of long-range information for molecular structure, we sought to understand the consequences of the harmonic prior for docking results. We found that the most-recent-at-the-time-of-our-initial-writing method often provides compressed poses, and there is some correlation between this compression and docking performance (though results changed with a newer version). We retrained the method to use a prior incorporating information from a molecular conformation, to determine whether a prior with more comprehensive structural detail would provide better performance. Performance did not improve with this new prior, whether the exact long-range information was used or whether noise was added. This finding suggests that further prior development is unlikely to improve performance, implying perhaps advances in the neural network could be another avenue to consider. Therefore, we discuss some possible ways to leverage local and long-range structural information in the neural network. By understanding chemical features associated with docking performance, investigating results with a more chemically-informed prior, and suggesting possible neural network advances, this work enhances the molecular machine learning community's grasp of the repertoire of opportunities available to improve docking performance.

1 INTRODUCTION

In a rewarding but challenging drug discovery journey,(Kola & Landis, 2004) structural information can help illuminate the path forward.(Blundell, 1996) Viewing how a protein interacts with a target ligand can catalyze progress in drug design: by seeing the structure, a medicinal chemist can generate ideas for new molecules with enhanced interactions.(Greer et al., 1994) Experimentally obtaining structures can be resource-intensive. Molecular docking employs *in silico* techniques to generate a structure of a protein-ligand complex, providing critical structural information with lower cost.(Shoichet et al., 2002) Traditionally, docking methods were physics-based, employing first principles governing intermolecular interactions in order to predict a ligand's pose.(Friesner et al., 2004) While helpful, these methods simplify the underlying physics, which can limit output quality.

Machine learning methods offer a promising alternative. Instead of hard-coding in particular physics, they learn from the available data, analyzing input protein-ligand complexes in order to grasp the principles governing protein-ligand interactions. Recently, generative models have demonstrated strong docking performance.(Corso et al., 2022; Stärk et al., 2023) HarmonicFlow (HF) is a

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flow-matching generative model, learning a vector field to find the ligand pose.(Stärk et al., 2023) This method, although representing an improvement over others, does not provide root-mean-square deviations (RMSDs) under 2 Å of the correct pose in over half of cases even when the pocket is defined (Stärk et al., 2023), offering opportunities for further improvement.

Previous diffusion-based docking models (Corso et al., 2022) sample from a Gaussian, then denoise the chosen parameters to find the docking pose. Flow matching algorithms, on the other hand, learn the flow field between the initial and the true data distribution. This allows the model to use an informative prior as input instead of a Gaussian. An informative prior will provide positive inductive bias for the flow-matching process.

The current flow-matching algorithm for ligand docking employs a harmonic prior, sampling bonded atoms near each other.(Jing et al., 2023) We noted that this prior would therefore neglect longer-range information. This observation motivated two lines of inquiry discussed in this paper. First, we sought to understand the possible consequences of the loss of long-range information for poses and for docking performance. Second, we modified the HF prior to incorporate long-range information and compared performance across priors. We present both of these investigations and then share some possible future avenues based on the results and further structural analysis.

2 METHODS

The training, validation, and test sets were from PDBbind (Liu et al., 2017), using a time split. Distance-Pocket was used to define the binding pocket. We experimented with an additional informative prior that uses RDKit(rdk), an open-source toolkit for cheminformatics, to calculate the atomic coordinates in the ligand. We used RDKit to sample a different conformer as a prior each time. RDKit generates the conformer coordinates using distance geometry. RDKit first calculates the molecule bounds matrix that contains minimum and maximum distances between pairs of atoms based on bonds in the molecule. It then uses this information to generate a random distance matrix that is consistent with the calculated bounds. The distance matrix is used to produce the 3D coordinates of the molecule, and different random distance matrices derive different structures when RDKit samples them. The Universal Force Field (Rappé et al., 1992) was used to clean up the generated conformers. (Landrum, 2012) We also experimented with a prior that adds Gaussian noise to the coordinates generated by RDKit. While RDKit samples different priors when generating conformers, adding Gaussian noise to the RDKit prior adds further randomness. This increases the variety of conformers accessibly sampled from the starting distribution, allowing a deeper exploration of the prior distribution space. We retrained HarmonicFlow RDKit and RDKit with Gaussian noise priors and benchmarked against the Gaussian and harmonic priors in the original work. Each model was trained with a batch size of 8 and 200 epochs. RMSD of the docked ligand pose compared to PDBbind was used to analyze docking performance. There were 268 ligands in the test set used after preprocessing.

RMSD was analyzed in two different ways for the analysis. In 3.1 and 3.3, RMSD for each complex was computed for one output pose out of the samples, so that analysis could be connected to a single structure. Meanwhile, in 3.2, from the HF output, a summary of test set RMSD performance was found directly from the HarmonicFlow output (working from all samples). In both cases, RMSD was relative to the PDBbind ligand, and no symmetry adjustment was applied. From each complex identity, features describing the ligand could be computed from the processed PDBbind data provided in the HF GitHub Zenodo link. RDKit (rdk) was used to calculate ligand features. Conformers for the consensus analysis in 3.3 were generated with RDKit ETKDGv2 (Riniker & Landrum, 2015), following a procedure adapted from earlier work. (Stärk et al., 2022) Several modifications were made, including making conformer generation deterministic to aid analysis. This represents a slightly different procedure than that used for the retraining in 3.2.

3 RESULTS

We note that we present here results for the most recent HarmonicFlow workflow on GitHub at the time of writing this paper. Recently, an updated workflow was reported that led to significantly different results. We focus in the main text on the earlier results, due to how they illustrate opportunities to obtain a structural perspective on machine learning model output. Appendix Figure

6 presents results with the updated workflow. We believe this snapshot-in-time of our perspective while writing the paper could provide suggestions for encoding molecular information in machine learning methods which transcend this particular case study.

3.1 Drivers of HarmonicFlow with Harmonic Prior Docking Performance

In light of the harmonic prior's only incorporating local information, we sought to investigate: how well do ligands with more long-range information perform in docking? We found that there is a slight association between ligand heavy atom count and HF performance (Figure 7a). (HarmonicFlow discussed in this section refers to HarmonicFlow with a harmonic prior: we focused on this prior because of its extensive use in earlier work. (Stärk et al., 2023)) Intuitively, larger ligand size should correspond to higher count of non-local contacts (i.e., larger ligands have larger counts of atom pairs not directly bonded to each other). Another relevant type of long-range information is count of rotatable bonds, measuring flexibility of the ligand. We found that there is not much association between ligand rotatable bond count and HF performance (Figure 7b), though the association is in the direction of higher rotatable bond count with worse RMSD performance. Thus, loss of long-range information for the initial HarmonicFlow structures appears slightly more deleterious for larger ligands: because they are larger, non-local information could be more relevant.

To further understand possible structural underpinnings of RMSD performance, we considered the consequences of the lack of long-range information for the output predicted structure poses. The initial harmonic prior produces a quite compressed structure. (Stärk et al., 2023) To what extent does the final pose retain some folded-in character? We compared the radius of gyration of the PDBbind ligand structure with the HF-predicted ligand structure. Radius of gyration is a geometric parameter which can be interpreted as measuring the extent of dispersion of a set of points, such as atoms of a molecule. (Lobanov et al., 2008) We calculated the percent error of the radius of gyration for the HF-predicted ligand structure, compared to the PDBbind ligand structure. Percent error helps avoid possible confounding issues due to size effects. We found that many of the HF-predicted poses have a negative radius of gyration percent error, meaning that HF is predicting poses which are more compact, or folded-in, compared to the actual crystal structure poses (Figure 1b).

Furthermore, we found that higher over-estimation of compactness is associated with worse RMSD performance (Figure 1c), but not with heavy atom count (Figure 9c). The explanation could be that HarmonicFlow begins with quite folded-in structures, with steric repulsions. While the inference process should help unfold the structure, there seems to still be some folded-in quality retained. We note that the updated HarmonicFlow method led to reduced compression (Figure 6a): although the update occurred for other reasons, our independently finding this compression highlights how chemical intuition-driven analysis workflows can provide insights relevant to further machine learning methods development. This finding further motivated our existing interest in incorporating long-range information into the HarmonicFlow prior: could starting with more extended structures improve performance?

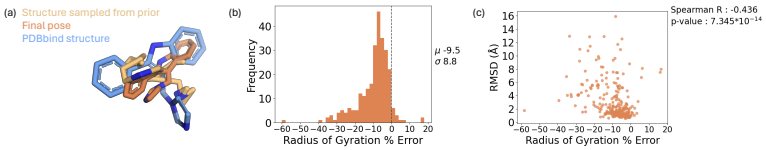

Figure 1: (a) 6PYA (Round et al., 2020) Structure sampled from the prior, final pose, and PDBbind pose (aligned with "fit" in PyMOL(LLC) to aid visualization). This structure was selected to illustrate compression, not to be representative. (b) Distribution of percent errors in radii of gyration (relative to PDBbind structure) from inference. (c) Scatterplot of RMSD with radius of gyration percent error. Appendix A.2.2 discusses p-value limitations and context of use.

3.2 Results for HarmonicFlow with a RDKit Prior

We calculated the RMSD on the test set for each model with different priors. RMSD < 2Å and Median RMSD are reported in Table 1. The results reveal that the harmonic prior still has the best

percentage of RMSD < 2Å and lowest median RMSD. RDKit has the worst performance in both metrics, indicating that using an RDKit prior might provide negative inductive bias to the model. However, the RDKit with noise prior outperforms the Gaussian prior in both metrics, implying introducing additional randomness to the RDKit prior could provide positive inductive bias. All of the priors underestimate radius of gyration (Figure 2).

	RMSD < 2Å	MEDIAN RMSD
GAUSSIAN	47.5	2.09
HARMONIC	53.7	1.83
RDKIT	44.8	2.29
RDKIT W/ NOISE	48.8	2.05

Table 1: **Comparison of different priors.** RMSD < 2Å is the percentage of predictions that have an RMSD to the ground truth within 2Å. Median RMSD is the median RMSD to the ground truth.

3.3 ANALYSIS OF STRUCTURES SUGGESTS POSSIBLE FUTURE DIRECTIONS

This work considers priors with a range of amounts of information. The similarity of performance for these priors with vastly different amounts of information suggests that further developing a prior based on a single structure is unlikely to yield a meaningful performance improvement. Furthermore, the finding that priors with long-range structures underestimate radius of gyration (Figure 2) suggests that long-range prior information is not sufficient for avoiding compressed poses. Therefore, another possible route to improve performance could be to incorporate additional information outside of the prior, such as into the neural network architecture. A prior is a starting point, so it should not meaningfully influence how compressed a final pose is. Incorporating information to help prevent compression across the pose generation process, not only at the start, is therefore a possible direction.

This section describes initial preliminary analyses to investigate: how can chemical understanding provide relevant information for the neural network? In light of the graph representation of the molecule employed, pairwise distance data represents a particularly promising resource. Because the atoms are already represented as nodes, and a framework exists to encode information regarding pairs of atoms as edges, pairwise information is particularly compatible with the model architecture. Stärk et al. (2023) While the current graph representation does incorporate distance information from ligand positions during inference in edges, the underestimated radii of gyration raise the question of whether richer distance information could be helpful. We present some thoughts first on bond distances, then on longer-range distances. We emphasize that the goal is to share general observations to guide future method development, and that we have not yet tested possible advances suggested in this forward-looking brainstorming section. In this section, HarmonicFlow refers to HarmonicFlow with a harmonic prior, and test set ligands were analyzed. While the updated HarmonicFlow workflow provides different results (Figure 6), we present results with the earlier method, as discussed further at the start of Section 3.

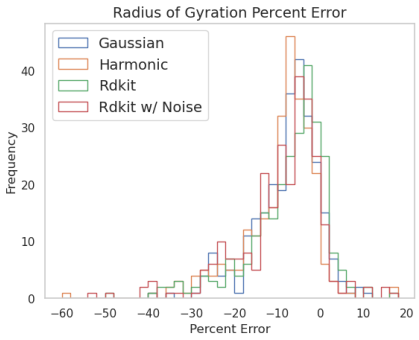

Figure 2: Comparison of radius of gyration. Percentage error of radius of gyration is calculated using the PDBbind structure as a reference. The radius of gyration percentage error is calculated for each different prior.

We found that HarmonicFlow underestimates bond lengths, relative to the PDBbind structures (Figure 3a), and that there are very often negative bond length percent errors. We found the average bond length percent error for each structure, to summarize the extent of this underestimation. It is correlated with both radius of gyration percent error and RMSD (Figure 3b). This correlation between bond length underestimation and performance raises the question: if only bonded information was in the prior, as is the case in the current harmonic prior, but chemically correct bond length information was provided outside the prior (elsewhere in the architecture), would RMSD performance improve? One further direction could be to include information in the neural network input

graph bonded atom edges about bond distances based on chemical knowledge of bond lengths from element and hybridization information.

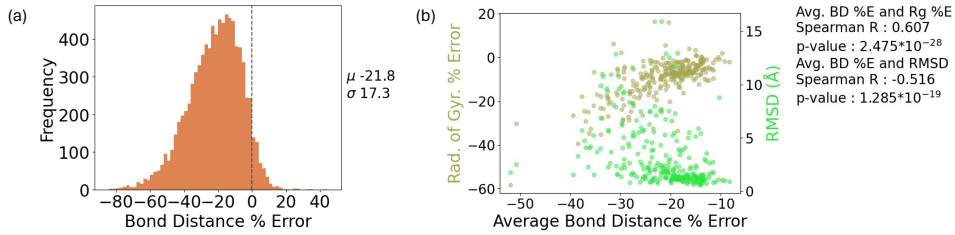

Figure 3: (a) Percent error of HarmonicFlow individual bond distances relative to PDBbind values. (b) Scatterplot of each complex's average HarmonicFlow bond distance percent error with RMSD and radius of gyration percent error.

We investigated whether an RDKit-generated conformer ensemble could provide longer-range distance information relevant to the final ligand pose. For each ligand, we generated 10 RDKit conformers. Because bond distances and angles should be expected to vary little (by chemical intuition), we focused on atoms separated by a torsion or more (over 2 bonds away from each other). For each such pair of atoms, we found the pairwise distance in each conformer (Figure 4). We computed the standard deviation of each such pairwise distance across conformers. There exists a wide spread of these standard deviations (Figure 11). Pairwise distance uncertainty may be relevant to neural network architecture. One possibility is high certainty (low standard deviation across conformers) information could be incorporated, so that distance information that is inferred from the conformers to be non-controversial helps guide the model. A second possibility is low certainty (high standard deviation) information could also help the model understand opportunities for flexibility in the molecule. For this paper, we focus on high certainty pairwise distances, though there may also be insight to be gained from other pairwise distances.

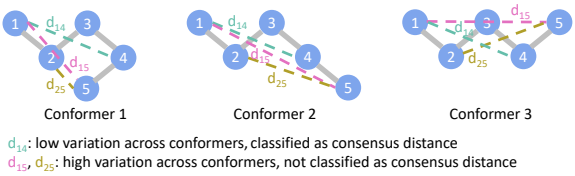

Figure 4: Conformer consensus distance analysis schematic

Those pairwise distances with low variation (standard deviation under 0.10 Å) across conformers were selected to represent our consensus distances (Figure 4): conformers are in approximate agreement on their value. The existence of consensus distances is quite common, with 94% of structures having at least 5 consensus distances (Figure 5a). We found that these consensus distances have low percent error when comparing their average values (across conformers) and the corresponding value for the distance between the same atom pair in the PDBbind ligand pose. Furthermore, in the HarmonicFlow pose, these same distances are often significantly underestimated (Figure 5b). A further direction could be to incorporate into the neural network input graph edges information corresponding to these consensus distances, thus including insights from the agreement between conformers which are both longer-range and likely to be accurate. This initial preliminary analysis focused on the output of conformer generation, and we also note that the distance geometry field (Havel, 1998; Blaney & Dixon, 1994), including the conceptual foundation of ETKDG approach (Riniker & Landrum, 2015), could be an area poised to contribute to future work. Further review of this literature could be fruitful. It is possible distance geometry information could be directly relevant to the neural network edges, without conformer generation acting as an intermediary of sorts. Also, it is likely (by chemical intuition) a number of these consensus distances correspond to aromatic rings: if this is the case, adding aromatic ring geometric information to the neural network may be another approach.

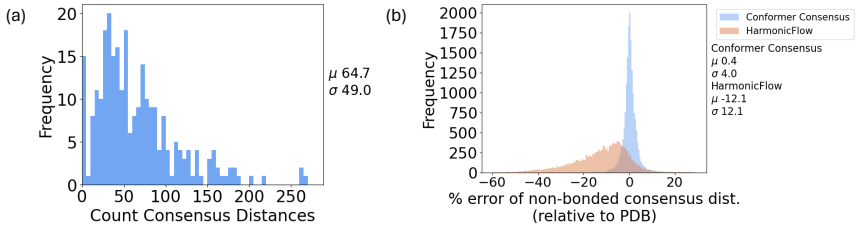

Figure 5: (a) Count of consensus distances in each structure. (b) Distribution of consensus distance percent error, with PDBbind as the reference, for the RDKit conformer ensemble's average distance value and for HarmonicFlow.

4 Limitations and Future Work

One limitation of this study is in the test set. It contains under 300 entries. A larger test set would enhance robustness of conclusions. Furthermore, the test, train, and validation dataset contains only ligand-protein complexes which have been reported to be amenable to structural characterization: speculating, possibly generalization to ligand-protein complexes which do not yield structures as easily may not be ideal. It would also be useful to analyze HarmonicFlow blind docking poses.

This work investigated the feasibility of the consensus distances concept but did not implement it in the neural network: such implementation is a possible future direction. Furthermore, investigating how consensus and non-consensus distance properties vary with other conformer generation methods (beyond RDKit), such as machine learning-based conformer generation approaches (Jing et al., 2022) is another possible direction, helping ascertain the sensitivity of consensus and non-consensus distance identification to conformer generation approach selection. In addition, an arbitrarily set threshold is currently employed to define consensus distances: one further step could be to more explicitly contextualize the standard deviation in the bonding framework by correcting for the number of bonds between atoms. While this work focused on consensus distances, developing a more nuanced understanding of non-consensus distances, such as analyzing variation patterns across conformers (e.g., bimodal versus a spread-out Gaussian), could help ascertain how to most effectively incorporate insights from these distances into the neural network.

We emphasize that, after the initial writing of this paper, the HarmonicFlow workflow was updated. This update, which was made independently of the work in this paper, led to less compressed poses (Figure 6). We believe the findings in this paper still remain of interest to the molecular machine learning community, because they present an illustration of the opportunities structural inspection offers to analyze methods' output. Although, in this case, the reduced compression occurred for other reasons, the analyses in this paper could have helped guide workflow development. Furthermore, as the molecular machine learning community develops additional innovative molecular representations of varying levels of complexity, incorporation of chemical knowledge, such as that described in Section 3.3, may be relevant for enhancing performance of other workflows.

5 Conclusion

The most-recent-at-the-time-of-initial-writing HarmonicFlow method with a harmonic prior produces compressed poses. Including longer range information does not improve flow matching results. Incorporating distance information from structural analysis into neural network architecture represents a possible future direction. By investigating the effect of priors on flow matching performance and suggesting neural network advances, this work expands the molecular machine learning community's understanding of how its toolbox can be leveraged for docking. These findings highlight the importance of taking a molecular-level glimpse into machine learning results; structural investigation can provide insights which may not always be available by statistics alone. In addition, the consensus distance approach brainstormed in this paper suggests the research community may want to reflect on how chemical and structural knowledge can inform model architecture. This work helps to understand the interplay between molecular structure and machine learning method performance, so that chemical insight can help enhance performance and accelerate drug discovery.

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A Appendix

A.1 Code Availability

Code can be accessed at: `https://github.com/hynsam/Flow_Matching_Docking_Analysis`.

A.2 Additional Methodological Details

A.2.1 Ligand Processing

All ligand files were checked to ensure that they only contain one molecule, and ligand files with more than one molecule were excluded. The PDBbind ligands were sanitized in RDKit, although the final poses were not due to RDKit errors encountered. While sanitizing in general changes some properties, our initial not-yet-comprehensive checks thus far have not indicated changes on sanitizing in properties which we compared between PDBbind ligands and final poses.

As mentioned above in the discussion of RMSD, symmetry and chemical equivalence across structures may be an issue for conformer pairwise distance standard deviations as well, and this is an area for possible future work. If a further symmetry adjustment does turn out to be necessary, that should only lower the standard deviations, so our impression is that the consensus distance analysis would reveal more consensus distances in this scenario.

A.2.2 Correlation Analysis and Plotting

To check correlations, we used the Spearman rank correlation coefficient. We note that the documentation(sci) mentioned p-values are only valid for more data points than we employed. We retain the p-values for qualitative general interpretation purposes, but we emphasize to the reader that the p-value is not entirely suitable here. The permutation analysis noted in the documentation is a possible area of future interest.(sci) While we made an effort to always include all data points in plots, we did sometimes truncate bounds when extreme values were present, to aid interpretation.

A.3 Possible Further Extensions

While this work is ligand-focused, considering protein-ligand interactions could be another possible future direction. We have carried out an initial preliminary PoseCheck(Harris et al., 2023) study of results from another HarmonicFlow run and compared to DiffDock PoseCheck results. While differences between the methods' settings complicate a direct comparison, we noted that the HarmonicFlow run did have fewer steric clashes as determined by PoseCheck. These fewer clashes may be due to the aforementioned pose compression. Comparing protein-ligand interactions in HarmonicFlow output versus PDBbind structures, and further physical feasibility analysis, may yield

suggestions of additional neural network architecture updates for components relating to protein-ligand interactions.

A.4 Additional Figures

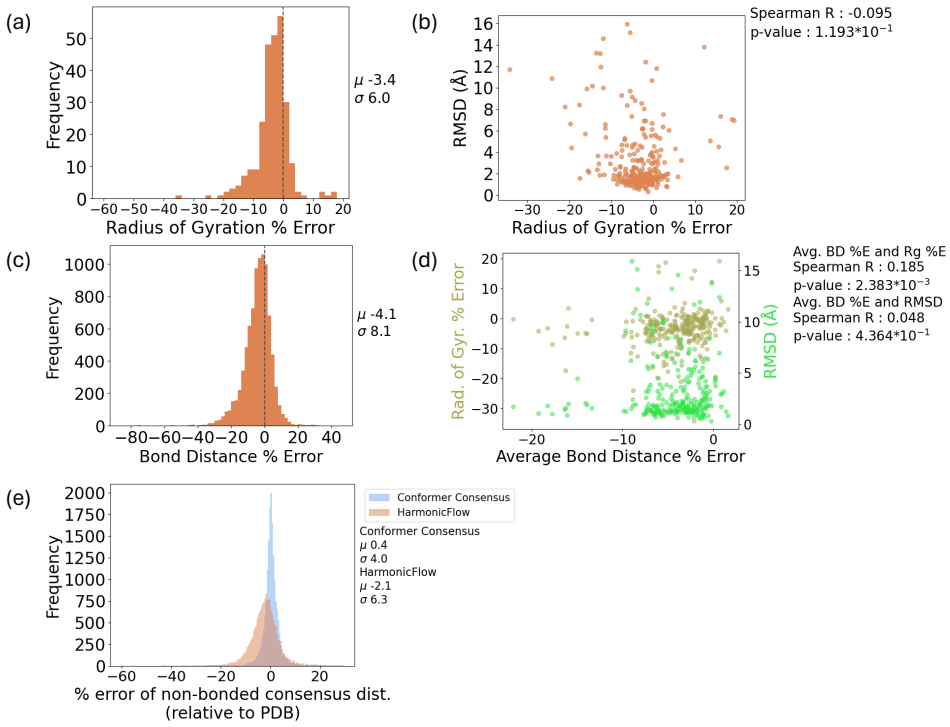

Figure 6: Results with latest HarmonicFlow method (a) Distribution of percent errors in radii of gyration from inference (percent error relative to PDBbind structure). (b) Scatterplot of RMSD with radius of gyration percent error. (c) Percent error of HarmonicFlow individual bond distances relative to PDBbind values. (d) Scatterplot of each complex's average HarmonicFlow bond distance percent error with RMSD and radius of gyration percent error. (e) Distribution of consensus distance percent error, with PDBbind as the reference, for the RDKit conformer ensemble's average distance value and for HarmonicFlow.

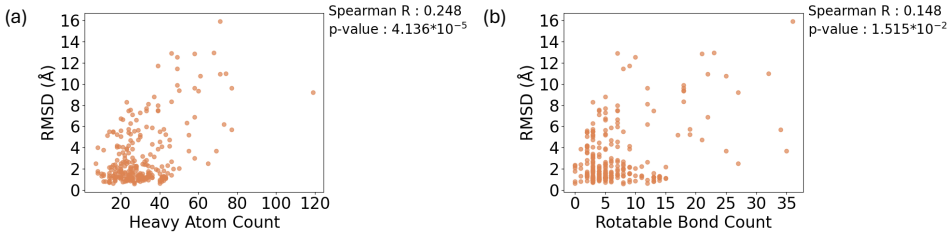

Figure 7: Scatterplot of RMSD and (a) ligand heavy atom count (b) ligand rotatable bond count

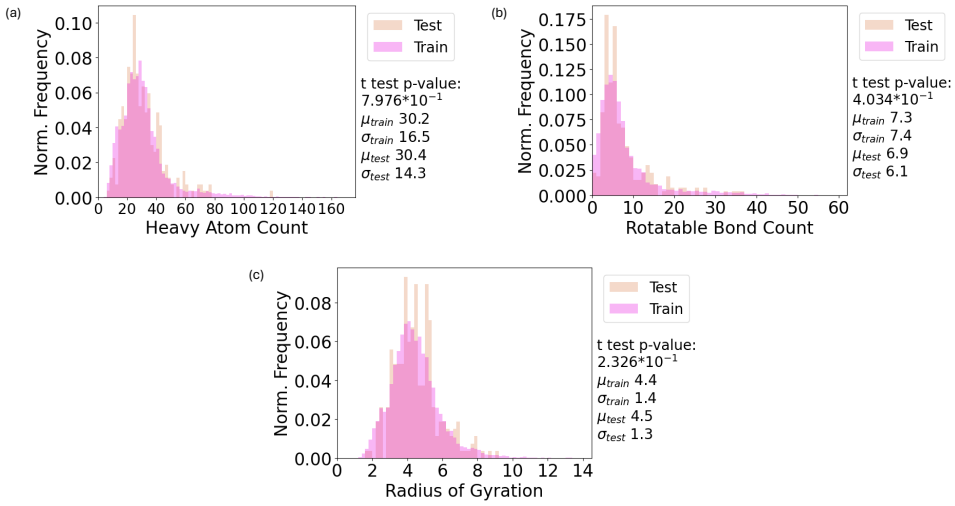

Figure 8: Distributions in the test and training sets of (a) heavy atom count, (b) rotatable bond count, and (c) radius of gyration. The t test p-value is used for approximate guidance, although suitability of the t test was not rigorously evaluated.

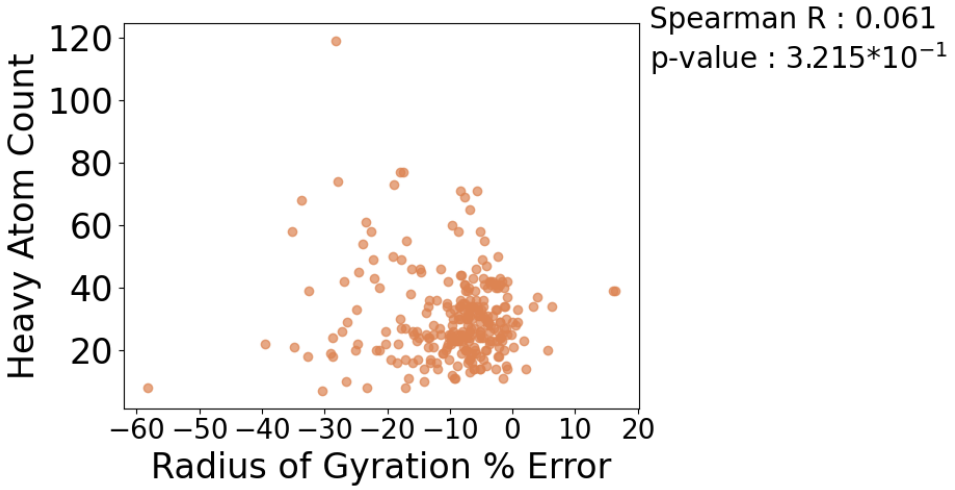

Figure 9: Scatterplot of radius of gyration and heavy atom count

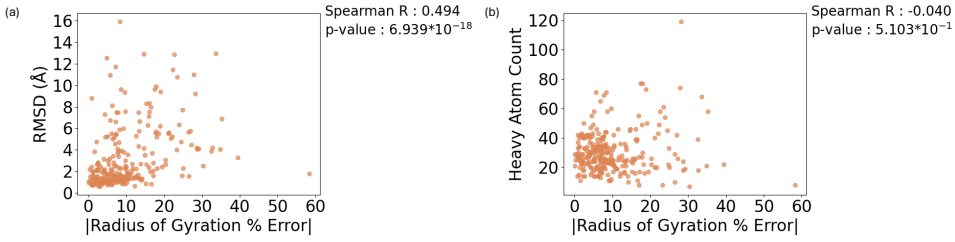

Figure 10: (a) Scatterplot of RMSD with absolute value of radius of gyration percent error. (b) Scatterplot of heavy atom count with absolute value of radius of gyration percent error.

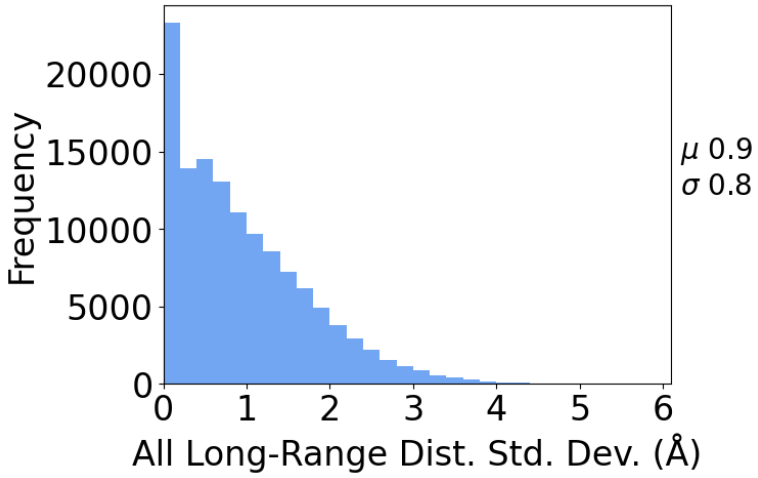

Figure 11: Distribution of all conformer ensemble standard deviations of pairwise distances of atoms separated by 3 or more bonds

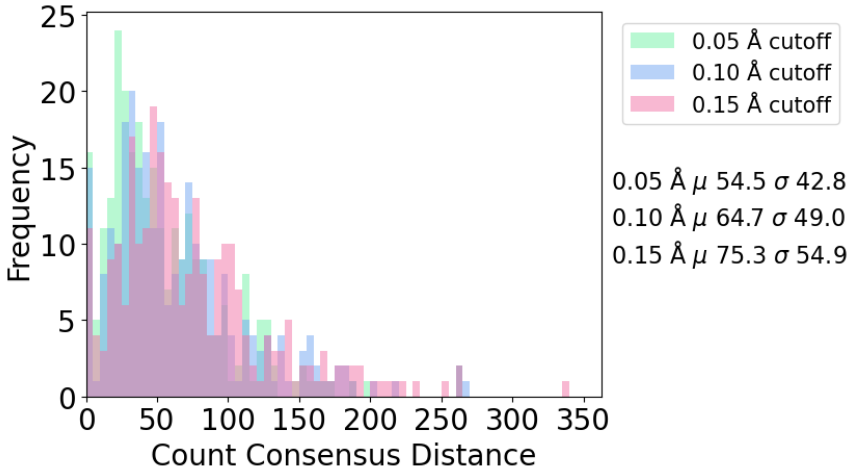

Figure 12: Consensus distance count distribution, for different consensus distance definition threshold values. These values differ only subtly from each other, and exploring a wider range of thresholds is a possible future direction.

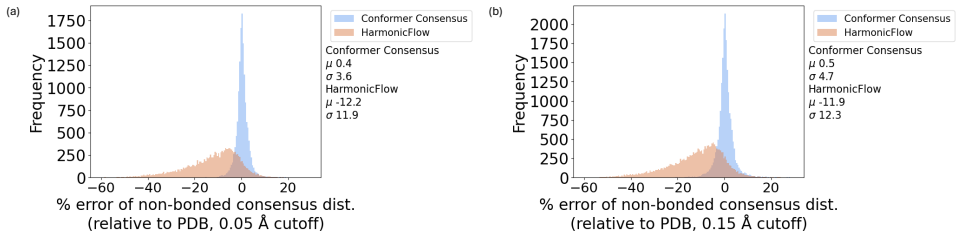

Figure 13: Consensus distance percent error (relative to PDBbind) comparison in the conformer ensemble's average distance value versus in HarmonicFlow, for different consensus distance definition threshold values. These values differ only subtly from each other, and exploring a wider range of thresholds is a possible future direction.