DiffDock-Site: A Novel Paradigm for Enhanced Protein-Ligand Predictions through Binding Site Identification

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Abstract

In the realm of computational drug discovery, molecular docking and ligand-binding site (LBS) identification stand as pivotal contributors, often influencing the direction of innovative drug development. DiffDock, a state-of-the-art method, is renowned for its molecular docking capabilities harnessing diffusion mechanisms. However, its computational demands, arising from its extensive score model designed to cater to a broad dynamic range for denoising score matching, can be challenging. To address this problem, we present DiffDock-Site, a novel paradigm that integrates the precision of PointSite for identifying and initializing the docking pocket. This two-stage strategy then refines the ligand's position, orientation, and rotatable bonds using a more concise score model than traditional DiffDock. By emphasizing the dynamic range around the pinpointed pocket center, our approach dramatically elevates both efficiency and accuracy in molecular docking. We achieve a substantial reduction in mean RMSD and centroid distance, from 7.5 to 5.2 and 5.5 to 2.9, respectively. Remarkably, our approach delivers these precision gains using only 1/6 of the model parameters and expends just 1/13 of the training time, underscoring its unmatched combination of computational efficiency and predictive accuracy.

1 Introduction

Protein-ligand interactions are pivotal in biological processes and play a crucial role in drug discovery endeavors [1]. While techniques like X-ray crystallography and Cryo-EM have granted deep insights into these interactions [2, 3], their associated costs and complexities have led to an increased dependence on computational methods, primarily molecular docking [4]. Established tools in this domain, such as Glide [9] and AutoDock Vina [10], have significantly advanced the field. Furthermore, molecular dynamics (MD) simulations continue to offer invaluable insights into biomolecular dynamics [5–8]. Nonetheless, despite these tools and advancements like binding free energy calculations [11–14], the quest for heightened accuracy and efficiency in docking is relentless. As we transition into an era dominated by deep learning, molecular docking techniques are set to undergo profound transformations.

The deep learning era has brought forth a paradigm shift in molecular docking techniques. Riding the wave of progress in geometric deep learning and generative modeling, molecular graph and

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geometry-based generative models have started to show immense potential in drug discovery [15–17]. Specifically, GeoDiff [18] employs diffusion models to navigate the vast chemical spaces, generating potential drug candidates. Similarly, DiffDock [19] harnesses the power of diffusion models but specifically tailors it for protein-ligand docking, offering a novel approach in the field.

While models like DiffDock have shown great promise, they often grapple with computational challenges, notably due to their intensive training requirements [19]. To address this problem, our study unveils DiffDock-Site, a novel two-stage molecular docking approach. In the initial phase, PointSite [20] is harnessed to pinpoint ligand-binding site (LBS) identification, ensuring precise ligand initialization in the docking pocket [20]. The subsequent phase employs a compact yet efficient scoring model tailored to refine the ligand's attributes. This bifurcated strategy strikes a balance between computational efficiency and predictive accuracy, offering an optimized solution in molecular docking. Specifically, our model parameters are 1/6 and training time 1/13 of traditional DiffDock, while the mean RMSD and centroid distance are reduced from 7.5 to 5.2 and 5.5 to 2.9, respectively.

2 Methodology

2.1 Overview

Our methodological approach is systematically visualized in Figure 1, providing a snapshot of the entire computational process. At its core, our method incorporates a two-stage molecular docking strategy. The initial phase revolves around PointSite, which we utilize for atom-level ligand-binding site (LBS) identification. Once the pocket of the protein is identified, the next stage is focused on the precise initialization of the ligand within this pocket. Subsequently, with the help of a more streamlined score model, we delve into the fine-tuning of the ligand's attributes, such as its location, orientation, and rotatable bonds.

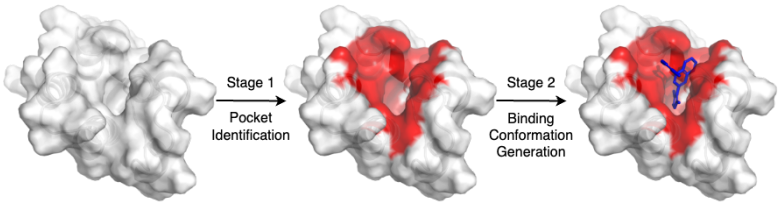

Figure 1: Overview of DiffDock-Site: A two-stage molecular docking paradigm. In Stage 1, PointSite identifies the protein's pocket, with the ligand subsequently initialized around the pocket's center. In Stage 2, the ligand's attributes are refined using a score model.

Following this overview, the subsequent sections delve deeper into each component, elucidating the intricacies of our approach and the underlying algorithms that power it.

2.2 Atom-Level LBS Identification via PointSite

To achieve accurate ligand docking, the initial identification of ligand-binding sites (LBS) is paramount. In our approach, PointSite serves as the primary tool for this pivotal step. Given a specific protein, PointSite interprets it at the atom level, representing it as point clouds. This conversion results in a coordinate matrix $X \in \mathcal{R}^{n\times 3}$, where n denotes the number of atoms. An accompanying feature matrix $F \in \mathcal{R}^{n\times 27}$ is derived from one-hot vectors, offering further granularity to the representation, as detailed in [20].

The output from PointSite, denoted as $Output \in [0,1]^n$, represents the probability of each atom being part of a binding site. Guided by these probabilities, the pocket center c is determined as the mean coordinate of atoms deemed highly probable binding sites (those with probabilities exceeding 0.5). This pocket center becomes pivotal in the subsequent ligand optimization phase.

2.3 Refinement of Ligand Attributes with Score Model

The precision in ligand docking is further refined using a generative model, inspired by the principles of diffusion mechanisms. Such models conceptualize data distribution as the starting point $p_0(\mathbf{x})$ of a forward diffusion process, as described by the Ito stochastic differential equation (SDE):

$$d\mathbf{x} = \mathbf{f}(\mathbf{x}, t)dt + g(t)d\mathbf{w}, \quad t \in (0, T) \tag{1}$$

where $\mathbf{w}$ denotes the Wiener process, and $\mathbf{f}(\mathbf{x}, t), g(t)$ are designated functions. The reverse process is also a diffusion process through the equation:

$$d\mathbf{x} = \left[\mathbf{f}\left(\mathbf{x}_t, t\right) - g^2(t)\nabla_{\mathbf{x}} \log p_t(\mathbf{x})\right] dt + g(t)d\overline{\mathbf{w}} \tag{2}$$

Following [19], we define a diffusion process over the degrees of freedom involved in docking: locating the binding pocket, its orientation in the pocket, and the torsion angles describing its conformation. And the perturbation kernels for these three are Gaussian, $IGSO(3)$ and wrapped normal distribution respectively. By using denoising score matching, the score network can be well trained for sampling. More details for the model are described in Appendix A.

By initializing the ligands around the identified pocket, the ligands' poses can be optimized by performing the reverse process as detailed in [21]. With this informative prior, the diffusion process is anchored to ensure that the ligand remains localized and highly relevant to the pocket of interest, which results in more focused and accurate ligand adjustments.

Moreover, using a compact score model makes the optimization process more computationally efficient without sacrificing predictive accuracy. The ligand attributes, including its position, orientation, and rotatable bonds, are honed with this approach, ensuring a docking that aligns well with actual biological interactions.

3 Experiments and Results

3.1 Experiment Settings

Dataset: We utilized protein-ligand complexes from PDBBind, originating from the Protein Data Bank (PDB) [22]. Adopting DiffDock's time-based split [23], we trained on 17k complexes up to 2018 and tested on 363 structures in 2019, ensuring no ligand overlaps. This temporal split is favored over molecular scaffold or protein similarity-based methods [24, 25].

Evaluating metrics: We follow prior work [23, 25] and use ligand root-mean-square deviation (RMSD) of heavy atomic positions and centroid distance to compare predicted binding structures with ground-truths. The Ligand RMSD calculates the normalized Frobenius norm of the two corresponding matrices of ligand coordinates. The centroid distance is defined as the distance between the averaged 3D coordinates of the predicted and ground-truth bound ligand atoms.

We implemented all the models using the open-source Python library PyTorch, and the experiments were conducted on a PC equipped with two NVIDIA A100 GPUs. More training details can be found in Appendix A.

3.2 Molecular Docking Quality Assessment

In our assessment of molecular docking quality, we benchmarked DiffDock-Site against several well-established methods, including SMINA [26], QuickVina-W [27], GLIDE [9], GNINA [28], Autodock Vina [10], EquiBind [23], TANKBind [25], and DiffDock [19]. The comparative performance metrics are detailed in Table 1.

Our proposed DiffDock-Site demonstrated commendable results, notably outperforming Diffdock in several metrics. Specifically, DiffDock-Site reduced the mean RMSD from 7.5 to 5.2 and boosted the percentage of ligands with RMSD values ≤ 5 Å from 62.4% to 64.8%. Furthermore, it improved the mean centroid distance, reducing it from 5.5 to 2.9, and increased the fraction of ligands with centroid distances ≤ 5 Å from 79.0% to 86.0%. It is worth pointing out that we trained our score model on two 40GB NVIDIA A100 GPUs for 400 epochs (around 2.8 days), which is much faster than

Method	Ligand RMSD						Centroid Distance					
	Percentiles↓				% Below		Percentiles↓				% Below	
	25%	50%	75%	Mean	2Å	5 Å	25%	50%	75%	Mean	2Å	5Å
QVINA-W	3.4	10.3	28.1	16.9	15.3	31.9	1.3	6.5	26.8	15.2	35.4	47.9
GNINA	4.5	13.4	27.8	16.7	13.9	27.8	2.0	10.1	27.0	15.1	25.7	39.5
SMINA	4.8	10.9	26.0	15.7	9.0	25.7	1.6	6.5	25.7	13.6	29.9	41.7
GLIDE	3.4	18.0	31.4	19.6	19.6	28.7	1.1	17.6	29.1	18.1	29.4	40.6
VINA	7.9	16.6	27.1	18.7	1.4	12.0	2.4	15.7	26.2	16.1	20.4	37.3
EQUIBIND	5.9	9.1	14.3	11.3	0.7	18.8	2.6	6.3	12.9	8.9	16.7	43.8
TANKBind	2.9	4.7	8.8	9.1	4.9	55.6	1.3	2.3	4.8	7.0	45.1	75.4
DiffDock	**1.4**	3.6	8.0	7.5	**38.4**	62.4	**0.5**	1.3	3.2	5.5	60.8	79.0
DiffDock-Site	1.6	3.6	6.7	**5.2**	33.96	**64.8**	0.6	1.4	2.8	**2.9**	63.6	**86.0**
DiffDock-Site-P	**1.4**	**3.4**	**6.2**	5.9	35.8	64.4	**0.5**	**1.1**	**2.6**	**3.9**	**65.0**	84.7

Table 1: Comparative Analysis of Top-1 PDBBind docking on Ligand RMSD and Centroid Distance Metrics Across Multiple Docking Algorithms.

conventional DiffDock (40 days). Moreover, the number of model parameters is 3.5 million, which is 1/6 of traditional DiffDock (20.24 million). However, it is worth noting that due to its streamlined design, boasting 1/10 of the parameters compared to Diffdock, DiffDock-Site falls slightly short in performance for the metric % RMSD $\leq$ 2 Å.

For a more comprehensive evaluation, we also tested a variant of our model, 'DiffDock-Site-P', which employed the pretrained Diffdock to refine ligand attributes. Impressively, 'DiffDock-Site-P' outperformed other models in most metrics, underscoring the advantage of initializing with identified docking pockets and then refining with a powerful predictor.

Figure 2 visually contrasts DiffDock-Site, DiffDock, and actual crystal structures for ligands 6s9w and 6uim. It's evident that DiffDock sometimes mispositions the ligand, causing overlaps with protein surfaces, as seen with 6uim. Conversely, our model showcases closer alignment to the crystal structures, highlighting its precision in molecular docking.

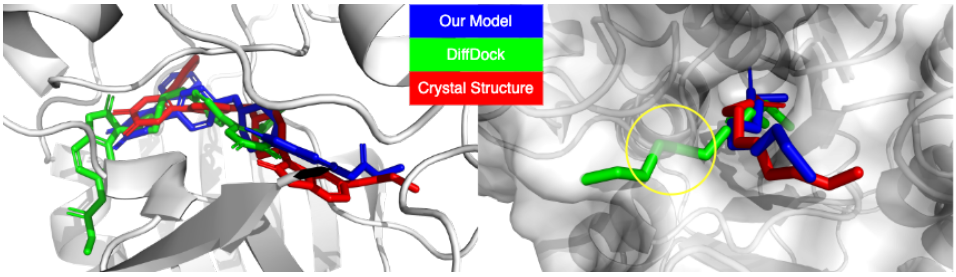

Figure 2: Comparative visualization of ligands 6s9w and 6uim (from left to right). Representations: Blue (DiffDock-Site), Green (DiffDock), and Red (Crystal Structure). Notably, with DiffDock, the ligand occasionally intersects with protein surfaces, as highlighted in the yellow circle for 6uim.

4 Discussion and Conclusion

We presented DiffDock-Site, a two-stage molecular docking paradigm that combines PointSite's ligand-binding site identification with a diffusion-based mechanism. The results showcased its superiority over state-of-the-art methods in accuracy and computational efficiency. While DiffDock-Site alleviates the computational demands of existing models like DiffDock to some extent, there is potential for further refinement. The current design isn't fully end-to-end, suggesting room for optimization. The notable performance of 'DiffDock-Site-P', which integrates pretrained DiffDock, hints at the benefits of leveraging existing models or knowledge bases in future iterations.

In conclusion, DiffDock-Site marks a significant advancement in molecular docking. Blending precision identification with efficient generative methodologies, it offers a promising platform for

drug discovery. With the continued intersection of AI and computational biology, platforms like DiffDock-Site are poised to reshape drug discovery endeavors.

5 Acknowledgments

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A Implementation details

A.1 Training Details

Our model's hyper-parameters were meticulously chosen to optimize performance. The specifics are tabulated below:

Parameter	Specification
Batch Size	Set to 32
Translation Parameters	$\sigma_{tr} \in [0.1, 5]$
Rotation Parameters	$\sigma_{rot} \in [\frac{\pi}{100}, \frac{\pi}{2}]$
Torsion Parameters	$\sigma_{tor} \in [\frac{\pi}{100}, \pi]$
Protein Graph Configuration	Max. neighbors: 24 Max. neighbor distance: 15
Dropout and Convolution	Dropout rate: 0.1 Convolution layers: 4 (32 scalar features, 6 vector features)
Optimizer	$Adam$ optimizer with learning rate: $1e-3$ for diffusion model During inference: EMA of weights (decay: 0.999)
Denoising Steps	20 steps on 500 validation complexes every 5 epochs Final model chosen based on highest RMSDs percentage < 2Å

A.2 Model Efficiency

Our score model was trained on two 40GB NVIDIA A100 GPUs, completing 400 epochs in approximately 2.8 days. This is a substantial improvement over the conventional DiffDock's 40-day training duration. Moreover, with only 3.5 million model parameters, DiffDock-Site achieves this efficiency while using just 1/6 of the parameters compared to DiffDock's 20.24 million.

A.3 Testset Considerations

An essential aspect of our methodology is the accurate identification of the Ligand Binding Site (LBS) by PointSite. If PointSite predicts an inaccurate LBS, the ligand cannot be optimized into the true pocket. For a set of specific PDB entries, the distances between the predicted pocket center and the ligand center exceed 20Å. As a result, these entries are excluded from the results presented in Table 1 as 'DiffDock-Site' and also in Table 2.

B Additional Results

In our effort to provide a comprehensive evaluation of DiffDock-Site, we further delved into a specialized analysis based on the top-5 PDBBind docking datasets. This segment offers a deeper comparative perspective, highlighting the intricacies and nuances that may not be immediately evident in broader benchmarks.

B.1 Ligand RMSD Analysis

The Root Mean Square Deviation (RMSD) of ligands provides crucial insights into the accuracy of predicted binding poses as compared to the true, experimentally determined positions. A lower RMSD value indicates a closer match to the experimental data, and thus, a better performance of the docking method.

Method	Ligand RMSD					Centroid Distance				
	Percentiles↓			% Below		Percentiles↓			% Below	
	25%	50%	75%	2Å	5 Å	25%	50%	75%	2Å	5Å
DiffDock	**1.2**	2.6	4.9	**44.8**	75.7	**0.4**	**0.9**	2.1	72.6	87.6
DiffDock-Site	1.3	2.5	**4.6**	42.0	**77.0**	0.5	1.0	2.1	72.3	**92.8**
DiffDock-Site-P	**1.2**	**2.4**	4.9	43.3	75.8	**0.4**	**0.9**	**2.0**	**73.9**	89.4

Table 2: Comparative Analysis of Top-5 PDBBind docking on Ligand RMSD and Centroid Distance.

From the results presented in Table 2, DiffDock-Site showcases competitive performance in ligand RMSD metrics. Especially when comparing the percentiles, DiffDock-Site consistently performs at par, if not better, than most traditional methods. The 25% and 50% percentiles, in particular, suggest that for a significant fraction of the dataset, our model's predictions are remarkably close to the actual poses.

B.2 Centroid Distance Analysis

Centroid distance, another pivotal metric, measures the deviation between the center of the predicted ligand pose and the center of the true ligand pose. A smaller centroid distance is indicative of a more accurate prediction.

As per the results in Table 2, DiffDock-Site excels in this metric as well. The model consistently yields lower centroid distances across all percentiles, emphasizing its ability to predict ligand poses that are not just geometrically accurate in orientation but also spatially well-positioned within the protein's active site.

B.3 Comparative Insights

While both DiffDock and DiffDock-Site demonstrate strong performances across the board, it's the 'DiffDock-Site-P' variant that stands out. By integrating the pretrained Diffdock for refining ligand attributes, 'DiffDock-Site-P' manages to outshine all other models in most metrics. This underscores the advantage of a two-stage approach: initially identifying the docking pockets and then refining the pose with a powerful predictive model.

In conclusion, these additional results not only validate the efficacy of DiffDock-Site but also highlight the potential areas where further refinement, especially with pre-trained models, can lead to even more accurate predictions.