DiffDock: Diffusion Steps, Twists, and Turns for Molecular Docking

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Molecular Docking Problem

- Biological function of proteins can be modulated by ligands binding to them.
- Molecular docking: predicting the position, orientation, and conformation of a ligand when bound to a target protein
- Approaches to docking:
  - Search-based methods: search space can be vast with rugged energy landscape
  - Deep learning methods: one-shot predictions that treat docking as regression problem. Much faster but no significant improvements in accuracy.

DiffDock

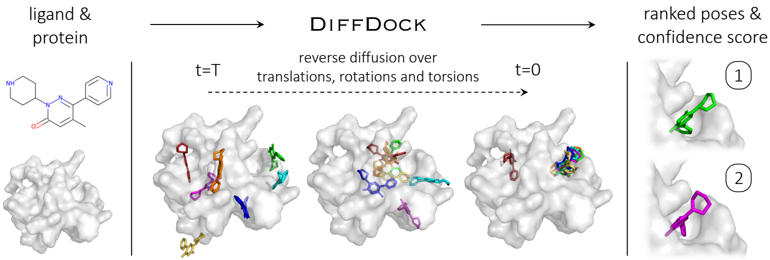

Figure: Overview of the DiffDock process [1]. Diffusion is carried out over the set of poses for a ligand. Then a confidence model is used to rank the potential poses.

Why use generative modeling?

- Regression models suffer when there is uncertainty as they will tend to average over the possibilities to reduce the expected error.
- Generative models can capture the distribution over the possible alternatives.

Problems with regression strategies

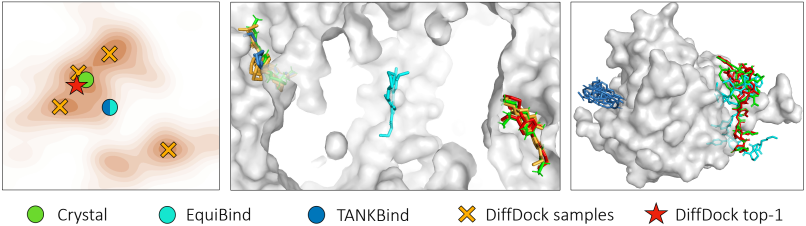

Figure: Uncertainty leads to regression models averaging over the possibilities. This leads to physically implausible poses and steric clashes.

Diffusion Scheme

- Want to diffuse on the set of ligand poses $\mathcal{M}_{\mathbf{c}}$, keeping the protein fixed.
- Given a seed conformation $\mathbf{c} \in \mathbb{R}^{3n}$ of the ligand, any pose can be reached by a combination of (1) translations, (2) rotations, and (3) changes to torsion angles.
  - Translations: $\mathbb{R}^3$
  - Torsion angles: $\mathbb{T}^m$
  - Rotations: $SO(3)$ (3×3 orthogonal matrices with determinant $= 1$)
- $\mathbb{P} := \mathbb{R}^3 \times SO(3) \times \mathbb{T}^m$
- $A : \mathbb{P} \times \mathbb{R}^{3n} \to \mathbb{R}^{3n}$ where $A(\cdot, \mathbf{c}) : \mathbb{P} \to \mathcal{M}_{\mathbf{c}}$ is a bijection
- Thus it's sufficient to define diffusion on $\mathbb{P}$.

Diffusion Kernel

- To efficiently implement denoising score matching, we need to know the diffusion kernel. Here we use exploding variance with independent noise in each coordinate.
- Since $\mathbb{P} : \mathbb{R}^3 \times SO(3) \times \mathbb{T}^m$ is a product manifold, we can find the diffusion kernel on each of its components [2]:
  - $\mathbb{R}^3 \longrightarrow$ normal distribution
  - $\mathbb{T}^m \longrightarrow$ wrapped normal
  - $SO(3) \longrightarrow IGSO(3)$ (can be efficiently compute by a truncated infinite series).

Model Architecture

- Score model $\mathbf{s}(\mathbf{x}, \mathbf{y}, t)$ outputs vectors on the tangent space $T_{\mathbf{r}}\mathbb{R}^3 \oplus T_R SO(3) \oplus T_{\boldsymbol{\theta}}\mathbb{T}^m$
  - Two $SE(3)$ equivariant vectors and one $SE(3)$ invariant vector
- Confidence model $\mathbf{d}(\mathbf{x}, \mathbf{y})$ predicts a single scalar that is $SE(3)$ invariant
- Score model operates on a coarse-grained representation of the protein with α-carbon atoms, while the confidence model operates on an all-atom structure.
- Structures are represented as heterogeneous geometric graphs
- Architectures are similar to $SE(3)$-equivariant convolutional networks over point clouds [3, 4].

Results

Table: The top half contains methods that directly find the pose; the bottom half those that use a pocket prediction method.

	Holo crystal proteins				Apo ESMFold proteins				
	Top-1 RMSD		Top-5 RMSD		Top-1 RMSD		Top-5 RMSD		Average
Method	%<2	Med.	%<2	Med.	%<2	Med.	%<2	Med.	Runtime (s)
GNINA	22.9	7.7	32.9	4.5	2.0	22.3	4.0	14.22	127
SMINA	18.7	7.1	29.3	4.6	3.4	15.4	6.9	10.0	126*
GLIDE	21.8	9.3							1405*
EquiBind	5.5	6.2	-	-	1.7	7.1	-	-	0.04
TANKBind	20.4	4.0	24.5	3.4	10.4	5.4	14.7	4.3	0.7/2.5
P2Rank+SMINA	20.4	6.9	33.2	4.4	4.6	10.0	10.3	7.0	126*
P2Rank+GNINA	28.8	5.5	38.3	3.4	8.6	11.2	12.8	7.2	127
EquiBind+SMINA	23.2	6.5	38.6	3.4	4.3	8.3	11.7	5.8	126*
EquiBind+GNINA	28.8	4.9	39.1	3.1	10.2	8.8	18.6	5.6	127
DiffDock (10)	35.0	3.6	40.7	2.65	**21.7**	**5.0**	**31.9**	**3.3**	10
DiffDock (40)	**38.2**	**3.3**	**44.7**	**2.40**	20.3	5.1	31.3	**3.3**	40

References I

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