Independent SE(3)-equivariant Models for Rigid Protein Docking

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Protein Complexes

• Two or more proteins with different functions interact and form larger machines, i.e. complexes
  - E.g. changes their biological functions
• Involved in most of the biological processes
• Very important for many problems such as drug design, protein engineering, anti-body generation, etc.
Body docking

- Docking: Given the structures of the individual proteins, predict 3D structures of protein-protein complexes

- Rigid Body Docking (our today’s focus):
  - Proteins are treated as rigid bodies

- Flexible Docking
  - Internal structure of a protein can deform, e.g., bond lengths and torsion angles change
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Rigid protein-protein docking

- Which geometrical and physical constraints for protein-protein docking?
- How to inject them in DL models?
Docking: Given the structures of the individual proteins, predict 3D structures of protein-protein complexes

Rigid Body Docking (our today’s focus):
- Proteins are treated as rigid bodies

Flexible Docking
- Internal structure of a protein can deform, e.g., bond lengths and torsion angles change
Rigid body docking

- Traditional Docking Methods (e.g. ATTRACTION)
  - Sample candidate structures
  - Rank with score function (manually designed or deep learning based)
  - Time consuming
  - Not guaranteed to predict accurate complex structures

- Accurate and efficient protein-protein docking is still a grand challenge in biochemistry.
Rigid body docking

\[
X_1 \in \mathbb{R}^{3 \times n}
\]

\[
X_2 \in \mathbb{R}^{3 \times m}
\]
Rigid body docking

Predict rotation and translation of the ligand

Ligand $X_1 \in \mathbb{R}^{3 \times n}$

Receptor $X_2 \in \mathbb{R}^{3 \times m}$

Complex $Z_{1,2} \in \mathbb{R}^{3 \times (n+m)}$
Rigid body docking

ligand $X_1 \in \mathbb{R}^{3 \times n}$

receptor $X_2 \in \mathbb{R}^{3 \times m}$

predict rotation and translation of the ligand

$R \in SO(3)$, $t \in \mathbb{R}^3$

$Z_1 = RX_1 + t$ and $Z_2 = X_2$

complex $Z_{1,2} \in \mathbb{R}^{3 \times (n+m)}$
Rigid body docking

Different initial placement: and roles swapped

\[
ligand \quad X_1' = Q_2 X_2 + g_2 \in \mathbb{R}^{3 \times m}
\]

\[
receptor \quad X_1' = Q_1 X_1 + g_1 \in \mathbb{R}^{3 \times n}
\]

\[
ligand \quad X_1 \in \mathbb{R}^{3 \times n}
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\[
receptor \quad X_2 \in \mathbb{R}^{3 \times m}
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\[R \in SO(3), t \in \mathbb{R}^3\]

\[Z_1 = RX_1 + t \text{ and } Z_2 = X_2\]

\[Z_{1,2} \in \mathbb{R}^{3 \times (n+m)}\]

predict rotation and translation of the ligand

complex
Rigid body docking

Different initial placement; and roles swapped

predict rotation and translation of the ligand

\[ R \in SO(3), \, t \in \mathbb{R}^3 \]

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predict rotation and translation of the ligand

\[ Z_{1,2} \in \mathbb{R}^{3 \times (n+m)} \]
Rigid body docking

Different initial placement: and roles swapped

\[ \begin{align*}
X_1 & \in \mathbb{R}^{3 \times n} \\
X_2 & \in \mathbb{R}^{3 \times m} \\
Q_2 & \in \mathbb{R}^{3 \times m} \\
Q_1 & \in \mathbb{R}^{3 \times n} \\
g_2 & \in \mathbb{R}^{3 \times m} \\
g_1 & \in \mathbb{R}^{3 \times n}
\end{align*} \]

Predict rotation and translation of the ligand

\[ \begin{align*}
R & \in SO(3), \ t \in \mathbb{R}^3 \\
Z_1 &= RX_1 + t, \text{ and } Z_2 = X_2
\end{align*} \]

Complex

\[ \begin{align*}
Z_{1,2} & \in \mathbb{R}^{3 \times (n+m)}
\end{align*} \]

Predict rotation and translation of the ligand

\[ \begin{align*}
R' & \in SO(3), \ t' \in \mathbb{R}^3 \\
Z_2' &= R'X_2' + t', \text{ and } Z_1' = X_1'
\end{align*} \]

Complex

\[ \begin{align*}
Z_{1,2}' & \in \mathbb{R}^{3 \times (n+m)}
\end{align*} \]
Rigid body docking

Different initial placement: and roles swapped

Identical after superimposition

Rigid body docking

Identical after superimposition
Rigid body docking

Identical after superimposition

Different initial placement: and roles swapped

We derive necessary and sufficient conditions for this to always hold. These will constrain our model.
Independently SE(3) Equivariant Graph Matching Networks (IEGMNs)

K-nearest neighbor graphs

\[ G_1 = (V_1, E_1) \]

\[ G_2 = (V_2, E_2) \]

ligand \( X_1 \in \mathbb{R}^{3 \times n} \)

receptor \( X_2 \in \mathbb{R}^{3 \times m} \)
Independently SE(3) Equivariant Graph Matching Networks (IEGMNs)

K-nearest neighbor graphs processed with intra- and inter-molecular messages

\[ G_1 = (V_1, E_1) \]

\[ G_2 = (V_2, E_2) \]

\[ X_1 \in \mathbb{R}^{3 \times n} \]

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Independently SE(3) Equivariant Graph Matching Networks (IEGMNs)

K-nearest neighbor graphs processed with \textit{intra} and \textit{inter}-molecular messages

\begin{align*}
\mathcal{G}_1 &= (\mathcal{V}_1, \mathcal{E}_1) \\
\mathcal{G}_2 &= (\mathcal{V}_2, \mathcal{E}_2)
\end{align*}

$\mathbf{X}_1 \in \mathbb{R}^{3 \times n}$

$\mathbf{X}_2 \in \mathbb{R}^{3 \times m}$
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\[ X_2 \in \mathbb{R}^{3 \times m} \]

Independent SE(3)-equivariance of node coordinate embeddings, but invariance of node feature embeddings
Keypoints for Binding Site Identification and Docking Prediction

- binding pocket points

$X^*_2$, $X^*_1$

True docked complex
Keypoints for Binding Site Identification and Docking Prediction

- binding pocket points

\[ X_1^* \rightarrow X_2^* \]

\[ P_1^* = P_2^* \]

*True docked complex*
Keypoints for Binding Site Identification and Docking Prediction

- binding pocket points

$X_1^*$ $X_2^*$

$P_1^* = P_2^*$

True docked complex

True binding pocket location available during train only

undocked / unbounded input structure
Keypoints for Binding Site Identification and Docking Prediction

- Keypoints obtained via multi-head attention from the IEGMN outputs

- Binding pocket points

- True docked complex

- True binding pocket location available during train only

- Undocked / unbounded input structure

\[ P_1^* = P_2^* \]
Keypoints for Binding Site Identification and Docking Prediction

- Keypoints obtained via multi-head attention from the IEGMN outputs
- Binding pocket keypoints
- Binding pocket keypoint alignment
- True docked complex
- True binding pocket location available during train only
- Undocked / unbounded input structure

\[ \mathbf{P}_1^* = \mathbf{P}_2^* \]
Keypoints for Binding Site Identification and Docking Prediction

- Keypoints obtained via multi-head attention from the IEGMN outputs

- Binding pocket points

- True docked complex

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- Undocked / unbounded input structure

- Predicted docked structure by superimposing keypoints \( Y_1 \) and \( Y_2 \)

- Undocked / unbounded input structure

\[ X_1^* = X_2^* \]

\[ P_1^* = P_2^* \]
Keypoints for Binding Site Identification and Docking Prediction

- Binding pocket points
- Keypoints obtained via multi-head attention from the IEGMN outputs

True docked complex $X_1^* = P_2^* = P_1^*$

Auxiliary loss for avoiding point cloud intersection $\mathcal{L}_{NI}$

Predicted docked structure by superimposing keypoints $Y_1$ and $Y_2$

$Y_2 = RY_1 + t$

$X_2$

True binding pocket location available during train only

Undocked / unbounded input structure

$\mathcal{L}_{OT}$ binding pocket keypoint alignment
Keypoints for Binding Site Identification and Docking Prediction

- Keypoints obtained via multi-head attention from the IEGMN outputs
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- Undocked / unbounded input structure

Prediction error - ligand RMSD

Auxiliary loss for avoiding point cloud intersection
Keypoints for Binding Site Identification and Docking Prediction

- Keypoints obtained via multi-head attention from the IEGMN outputs
- Binding pocket keypoint alignment
- True docked complex
- True binding pocket location available during train only
- Predicted docked structure by superimposing keypoints $Y_1$ and $Y_2$
- Auxiliary loss for avoiding point cloud intersection

$P_1^* = P_2^*$

EquiDock

Prediction error - ligand RMSD

$X_1^*$

$X_2$

$Y_2 = RY_1 + t$

$RX_1 + t$

$\mathcal{L}_{MSE}$

$\mathcal{L}_{NI}$
Novel Surface Features

Inter residue force vector 

\[ w_{i,i'}(\lambda) (x_i - x_{i'}) \]

Normalized weighted force mean vector of length 

\[ \rho_i(x_i; \lambda) \]

a. Protein interior

b. Protein surface
Novel Surface Features

Normalized weighted force mean vector of length $\rho_i(x_i; \lambda)$

Inter residue force vector $w_{i,i',\lambda}(x_i - x_i')$

Protein interior

Protein surface

$$\rho_i(x_i; \lambda) = \frac{\left\| \sum_{i' \in N_i} w_{i,i',\lambda}(x_i - x_i') \right\|}{\sum_{i' \in N_i} w_{i,i',\lambda} \left\| x_i - x_i' \right\|},$$

where $w_{i,i',\lambda} = \frac{\exp\left(-||x_i - x_i'||^2/\lambda\right)}{\sum_{j \in N_i} \exp\left(-||x_i - x_j||^2/\lambda\right)}.$
Novel Surface Features

Special case: Equally distanced & infinite nearest neighbors

\[
\rho_i(x_i; \lambda) = \frac{2 \sin(\alpha/2)}{\alpha}
\]

Protein surface angle

α angle
Novel Surface Features

• Much faster than residue depth estimated with MSMS surface
• But how good is it?

Figure 6: Distribution of the Spearman rank-order coefficient computed per each protein as the correlation between MSMS residues’ depths and our surface features defined in Eq. (16) (for $\lambda = 30$). Histogram computed over the ligands in the DIPS test set (100 proteins).
Novel Surface Features

- Much faster than residue depth estimated with MSMS surface
- But how good is it?

$\lambda = 0.01$

$\lambda = 0.1$

$\lambda = 1$
# Datasets & Baselines

<table>
<thead>
<tr>
<th>Dataset</th>
<th># Pairs of Proteins</th>
<th># Residues per Protein</th>
<th># Atoms per Protein</th>
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</thead>
<tbody>
<tr>
<td>DIPS</td>
<td>41876</td>
<td>276 (±189)</td>
<td>2159 (±1495)</td>
</tr>
<tr>
<td>DB5.5</td>
<td>253</td>
<td>268 (±215)</td>
<td>2089 (±1694)</td>
</tr>
</tbody>
</table>

* DIPS dataset: biased towards rigid body docking (no unbound structures)

**Baselines:**
- **ClusPro**: protein-protein docking
- **PATCHDOCK**: Molecular Docking Algorithm Based on Shape Complementarity Principles
- **ATTRACT ONLINE**
- **HDOCK SERVER**: Protein-protein and protein-DNA/RNA docking based on a hybrid algorithm of template-based modeling and *ab initio* free docking.
Results and runtimes

Inference running time distributions (DIPS test)

C-RMSD distributions (DIPS test)

I-RMSD distributions (DIPS test)

Interface RMSD
Visualization

EquiDock
CRMSD = 7.13

PatchDock
CRMSD = 17.37

HDOCK
CRMSD = 18.00

ClusPro
CRMSD = 18.56

Ground Truth
PDB ID: 3DMP