Estimation of interfacial quality of protein complex models

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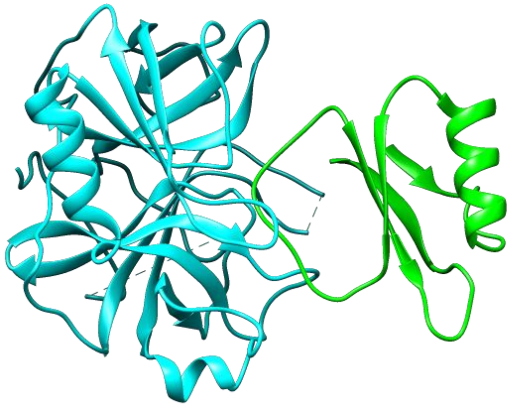
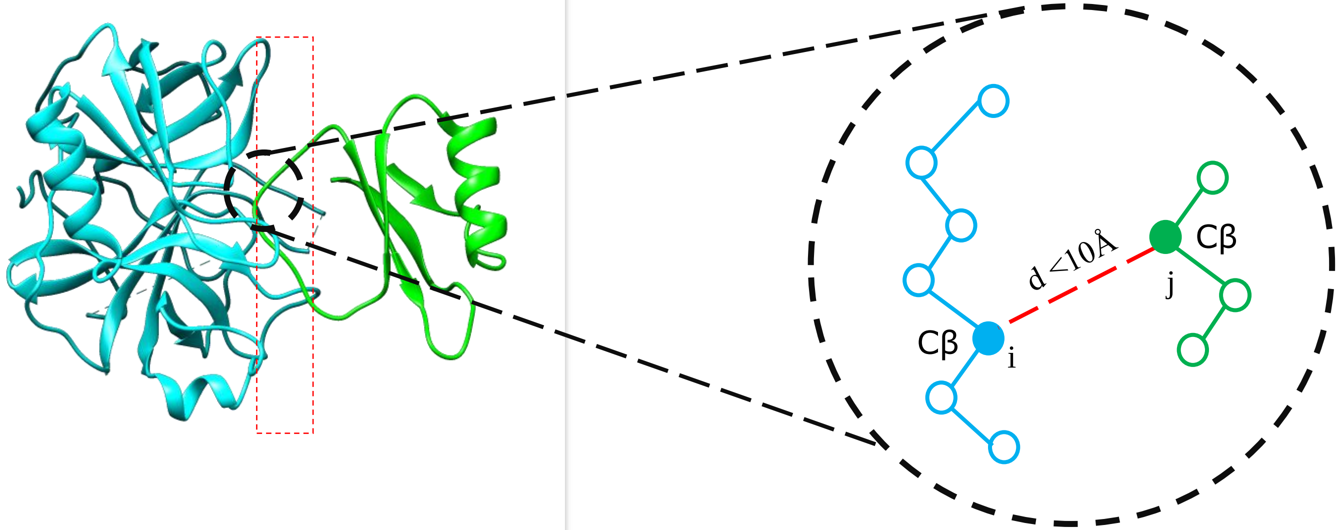
Background

Protein Complex



Crystal structure of 1ACB

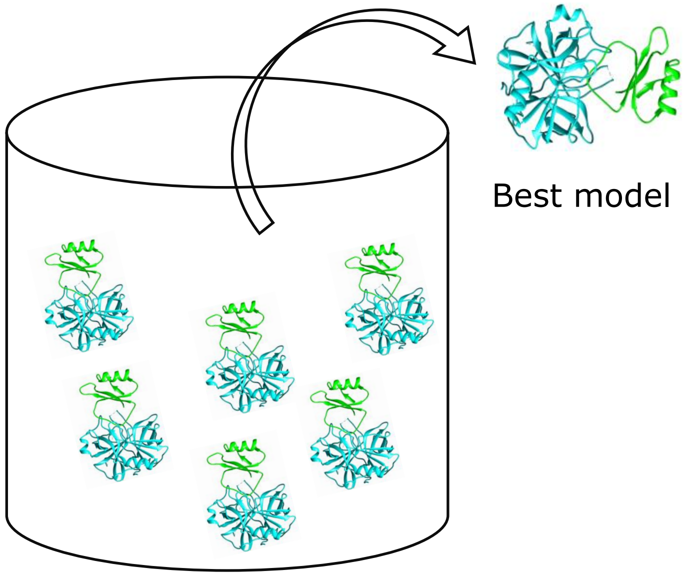
Interfacial region



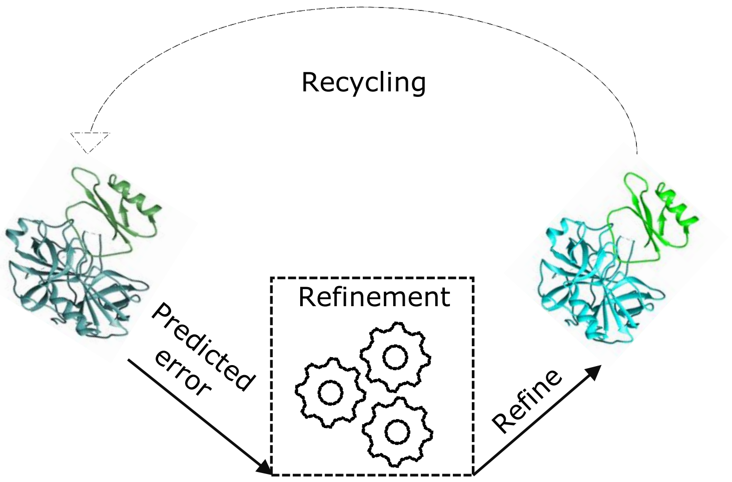
https://www.rcsb.org/structure/1ACB

Motivation

Model section



Model refinement



Helps in accurately guiding the process of protein complex prediction

Approach

- Dataset curation
- Feature extraction
- Model training
- Quality estimation

Dataset

Training

- Dockground docking decoy set v2
- 180 complex targets
- ~18000 docking decoys

Testing

- Dockground docking decoy set v1
- 23 complex targets
- ~2600 docking decoys

Feature extraction

- Node features (30)
  - Amino acids encoding (10)
  - Secondary structure (6)
  - solvent accessibility encoding (4)
  - Relative residue positioning (2)
  - MSA-based features (NEFF) (4)
  - Dihedral angles (4)
- Edge features (23)
  - Orientations between connecting nodes (theta, omega, phi) (6)
  - Edge distance encoding from 2 – 10 Å (17)

Learning algorithm

- Graph neural network
- Ideal for learning for graph representation
- Regression problem

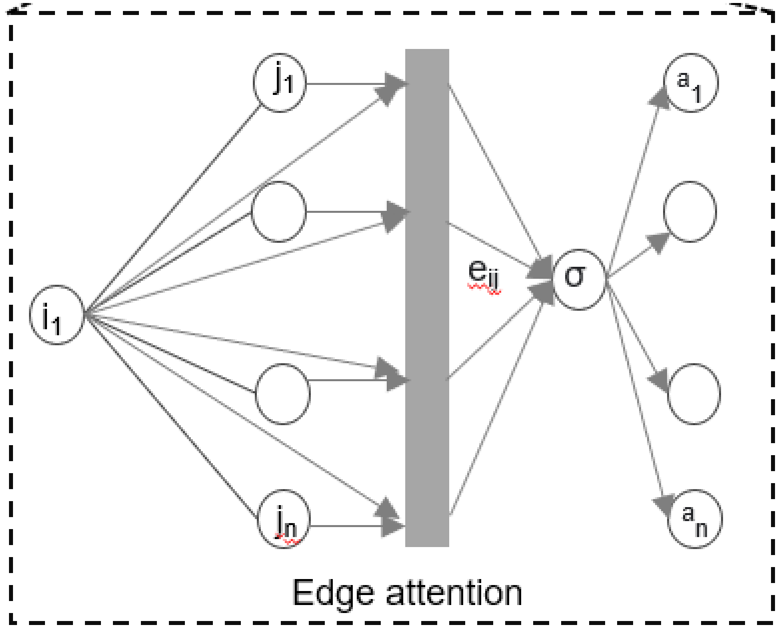
Graph attention network

GCN embedding

$$h_i^{(l+1)} = \sigma\left(\sum_{j\in\mathcal{N}(i)} \frac{1}{c_{ij}} W^{(l)} h_j^{(l)}\right)$$

$$c_{ij} = \sqrt{|\mathcal{N}(i)|}\sqrt{|\mathcal{N}(j)|}$$

GAT embedding



$$z_i^{(l)} = W^{(l)} h_i^{(l)}, \tag{1}$$

$$e_{ij}^{(l)} = \mathrm{LeakyReLU}(\vec{a}^{(l)^T}(z_i^{(l)} \| z_j^{(l)})), \tag{2}$$

$$\alpha_{ij}^{(l)} = \frac{\exp(e_{ij}^{(l)})}{\sum_{k\in\mathcal{N}(i)} \exp(e_{ik}^{(l)})}, \tag{3}$$

$$h_i^{(l+1)} = \sigma\left(\sum_{j\in\mathcal{N}(i)} \alpha_{ij}^{(l)} z_j^{(l)}\right), \tag{4}$$

Veličković,P. *et al., arXiv* (2018)

Multi-head attention

$$\text{concatenation}: h_i^{(l+1)} = ||_{k=1}^{K} \sigma \left(\sum_{j \in \mathcal{N}(i)} \alpha_{ij}^k W^k h_j^{(l)} \right)$$

$$\text{average}: h_i^{(l+1)} = \sigma \left(\frac{1}{K} \sum_{k=1}^{K} \sum_{j \in \mathcal{N}(i)} \alpha_{ij}^k W^k h_j^{(l)} \right)$$

Quality estimation

Target label

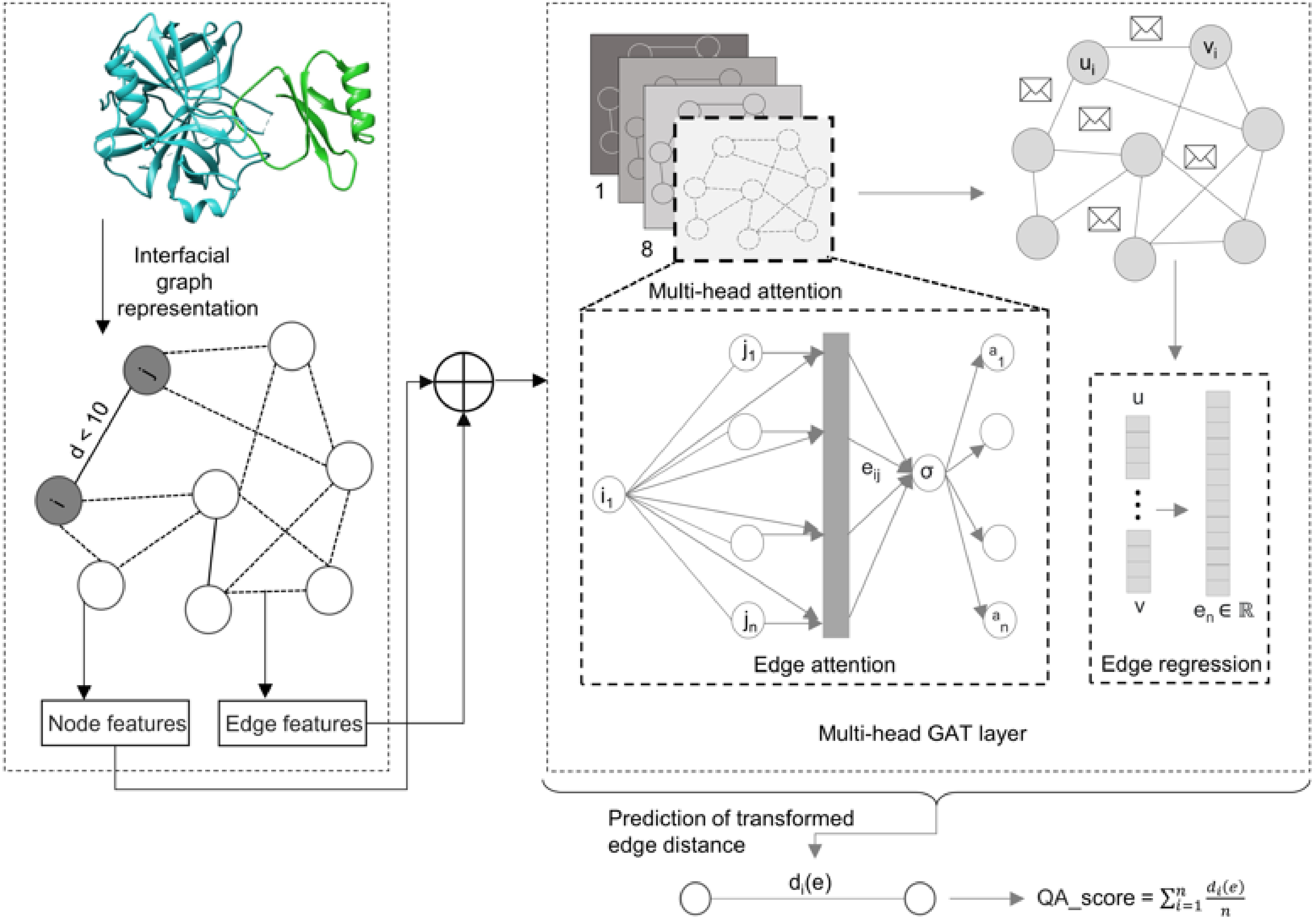
- For each edge (local quality)
- d_i = 10

$$s\_score = \frac{1}{1 + \left(\frac{d}{d_i}\right)^2}$$

- Global quality

$$global_{quality} = \frac{\sum_1^e s\_score_e}{n}$$

Flowchart



Interfacial
graph
representation
d < 10
Node features
Edge features
1
8
Multi-head attention
Edge attention
Edge regression
Multi-head GAT layer
Prediction of transformed
edge distance
QA_score = $\sum_{i=1}^{n} \frac{d_i(e)}{n}$

Model training

- Number of multi-headed GAT layers: 2
- Number of heads: 8
- Hidden dimension: 32
- Learning rate: 0.001
- Weight decay: 0.0005
- Loss: Mean Squared Error (MSE) with sum reduction
- Optimizer: Adam
- Number of batch: ~80
- Number of epochs: 500
- Patience: 40

Evaluation metrices

- Ground truth:
  - Observed s-score w.r.t iRMSD

$$s\_score = \frac{1}{1 + \left(\frac{d}{d_i}\right)^2}$$

- Pearson correlation between $\text{global}_{\text{quality}}$ and the s-score
- Spearman correlation between $\text{global}_{\text{quality}}$ and the s-score
- Kendall’s Tau correlation between $\text{global}_{\text{quality}}$ and the s-score

Competing methods

- DOVE_ATOM20
- DOVE_ATOM40
- DOVE_GOAP
- DOVE_ATOM_GOAP

Results

Dataset	Method	Avg. r	Avg. ρ	Avg. τ	Global r	Global ρ	Global τ
Dockground v1	**This work**	**0.441**	**0.314**	**0.224**	**0.531**	**0.593**	**0.421**
	DOVE_ATOM20	0.195	0.130	0.089	0.360	0.274	0.185
	DOVE_ATOM40	0.181	0.157	0.111	0.244	0.130	0.087
	DOVE_GOAP	0.084	0.140	0.094	-0.059	-0.085	-0.056
	DOVE_ATOM_GOAP	0.263	0.258	0.180	0.227	0.101	0.067

Contribution of GAT

Dataset	Method	Avg. r	Avg. ρ	Avg. τ	Global r	Global ρ	Global τ
Dockground v1	**GAT (This work)**	**0.441**	**0.314**	**0.224**	**0.531**	**0.593**	**0.421**
	GCN	0.284	0.223	0.156	0.412	0.451	0.311

Discussion and future plan

- Variable length graph
- Global and local quality

- Hyperparameter tuning
- Additional similar network
- Additional dataset
- Competing methods
- Additional accuracy metrics and case study

Challenges

- Variable length graph
- Regression problem

Reviewers' comments

- "It is representing only the interfacial region as a graph. But in decoys, there will be some orientations, where interface regions would be completely different compared to that of the corresponding native. I am wondering, if considering the interfacial region would cause some form of information loss. Therefore, considering the whole complex as a graph could provide more information during the learning process." (Computationally demanding, Pre-trained model, learning method, QA)
- "A visualization of the problem/dataset would be helpful to show the reader what exactly you'll be focusing on within the dataset." (Interfacial region, case study)
- "Can some node features be directly extracted from the interface coordinates themselves?" (Edge features, agreement)

Acknowledgement

Debswapna Bhattacharya, Ph.D.
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Virginia Tech

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