XGBoost Models to Evaluate 3D Ligand Representations

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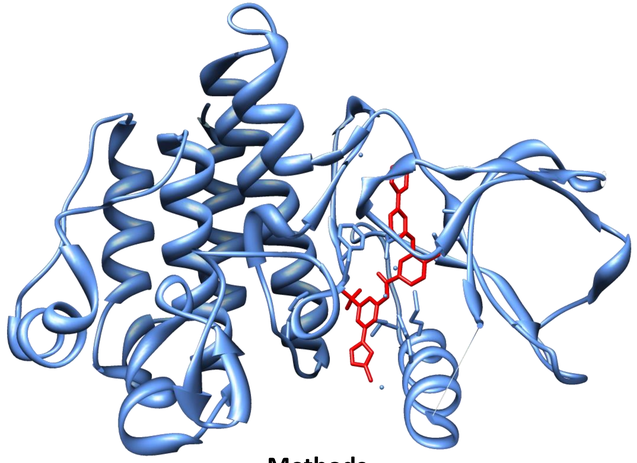
Motivations

Accurate 3D representations are key to training effective deep learning models.

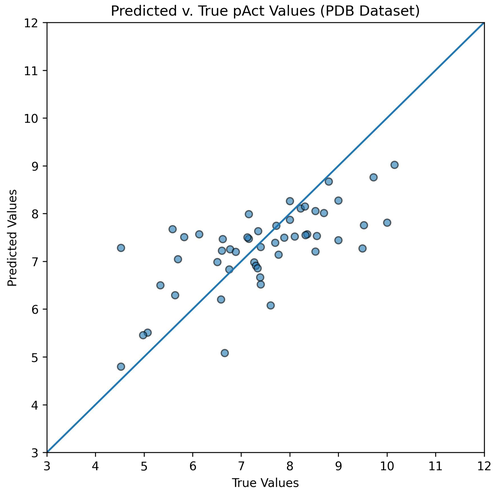
- Kinases are highly druggable biological targets broadly implicated in biological disorders.
- Previous work in the Karanicolas Lab has demonstrated the need for structure-based ligand representations.
- However, it is unclear if these 3D structure-based representations are accurate representations of the ground truth.

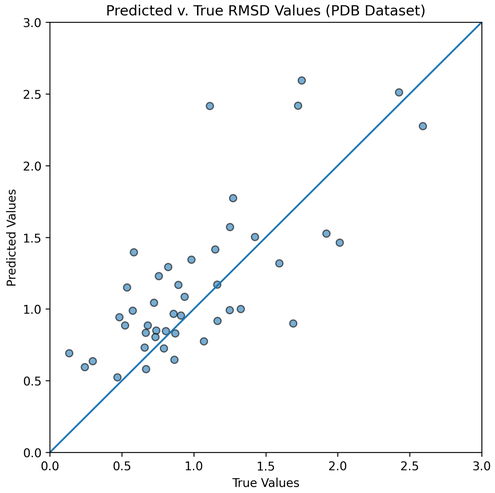


Methods

- We start with a curated subset of kinase-inhibitor complexes in the PDB with recorded binding affinity that are then standardized to pAct scores.
- Train XGBoost pipeline to predict binding affinity from energy features.
- We hypothesize that our pipeline will accurately predict pAct for models close to ground truth – we can then use this XGBoost pipeline to select between models when a PDB structure is unavailable.
- Features used:
  - Rosetta energy components
  - RDKit features
  - OpenEye Omega features

Results





Pipeline	Pearson R	MSE
Predicting RMSD on PDB Dataset	0.250	3.231
Predicting pAct on PDB Dataset	0.671	1.041

Discussion

- Our pipeline demonstrates competence on a range of tasks and is able to recapitulate both RMSD (especially at the lower ranges) and pAct.
- The ability to recapitulate pAct from energy features is a promising sign that our pipeline can discriminate between kinase-inhibitor models with poor RMSD.
- This is further evidenced by the fact that there is a performance decrease when we use the Christmann-Franck database that does not rely directly upon PDB structures (Pearson R: 0.354).

Future Directions

- Using similarity scores – such as Maximum Common Substructure – to cluster inhibitors so as to ensure minimal information leakage.
- Further filtering the data to ensure only models with a sufficiently small RMSD are used as training data
- Training on different sets of features – Rosetta energy components only or RDKit features only.

Acknowledgements

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