KinBADL: Developing a 3D CNN to Predict Kinase-Inhibitor Binding Affinity

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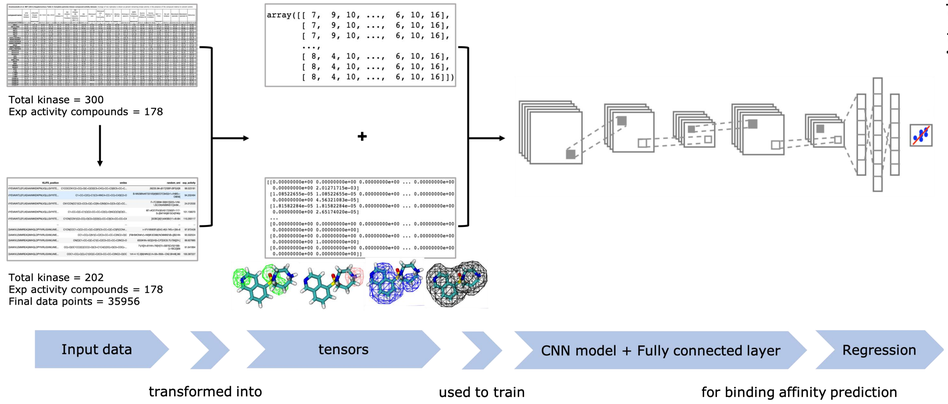
Motivations

How do we develop a generalizable deep learning model for predicting kinase-inhibitor binding affinities?

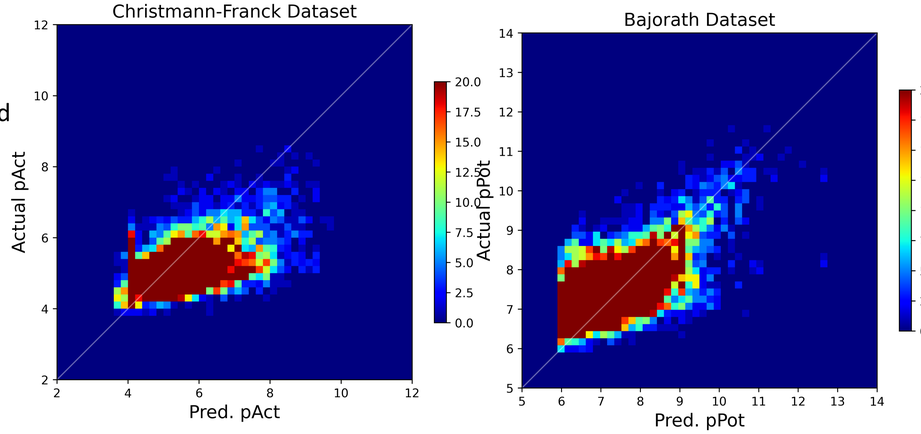
- Kinases are highly druggable biological targets broadly implicated in biological disorders.
- Developing a screening pipeline that can accurately identify kinase inhibitors will significantly streamline the screening of compound libraries.
- Previous work in the Karanicolas Lab has demonstrated the need for structure-based ligand representations.



Methods

- Ligand Representation: 3D Pharmacophores
  - Conformers for compound are generated, aligned with closest ligand in PDB.
  - The best aligned conformer is used to generate the 3D pharmacophore for model training
- Protein Representation: SeqVec and Onehot Encoded Representations from KLIFS sequences (ATP binding site).
  - SeqVec is a novel protein representation inspired by NLP model ELMo.
  - No difference between SeqVec and Onehot Enoded Representations
- Model Training
  - Training was conducted on both Argonne National Lab's GPU cluster and Google Colab.

Results



Dataset	Pearson R	MSE	RMSE	MAE	CI
Bajorath	0.672	0.579	0.760	0.580	0.724
Christmann-Franck	0.531	0.918	0.958	0.746	0.668

Discussion

- Our model performs comparably to others in the literature, exhibiting a lower MSE (RosENet: 1.24; Kdeep: 1.27).
- Our model also displays a surprisingly high concordance index – even if our model is not predicting actual binding affinities, it is able to preserve the rank of inhibitors in its predictions.
- Performance varies among kinases: e.g. PIM3 has Pearson Correlation of 0.79 and CDK9 has Person Correlation of 0.51
- The Bajorath dataset contains more ligand diversity than the Christmann-Franck dataset and is the likely cause of the performance differential.

Future Directions

- Rebuilding the Christmann-Franck dataset, filtering for compounds that have close analogues recorded in PDB.
- Using the top few conformers instead of solely the top 1 conformer.
- A transfer learning regime – first train our model to predict Rosetta Energies and use these weights as the starting point for binding affinity training.
- Adding a structural kinase representation.

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