Binding Affinity Prediction of Protein-Ligand complexes using Machine Learning

MSc Project

Abdus Salam Khazi

Supervisors:
Simon Bray & Alireza Khanteymoori

October 8, 2021

Table of Contents

1. Introduction
   - Biological Background
   - Problem Definition.
2. Machine Learning Pipeline
3. Data Processing
   - Data preprocessing
   - Feature Extraction & Selection
   - Measurement resolution
4. Machine Learning Models
   - Simple Linear Regression
   - Random Forest Regression
   - Support Vector Regression
   - Rotation Forest Regression
5. Testing strategy
6. Results
7. Discussion
8. Q & A
9. References

Biological Background

What are a proteins and ligands?

- **Proteins:** Complex molecules that are work-horses (machines) of a living organism.
- **Ligands:** Molecules that bind to particular proteins, called receptor proteins.
- Proteins and ligands bind together to form protein-ligand complexes.

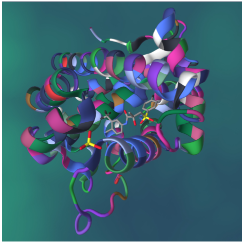


Figure: Haemoglobin transporter protein [?].

Biological Background

Protein-Ligand complexes

- Any potential binding location in the 3D structure of a protein is called a pocket.
- The pockets of proteins only bind to ligands of complementary shape.
- Drugs are just ligand molecules that bind to protein to cause a therapeutic effect.

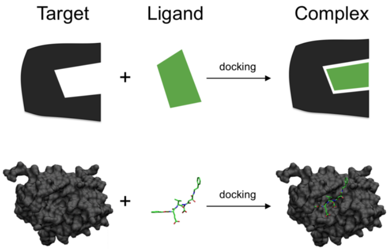


Figure: Lock and Key hypothesis in molecular docking [?].

Biological Background

Understanding Protein-Binding Affinity.

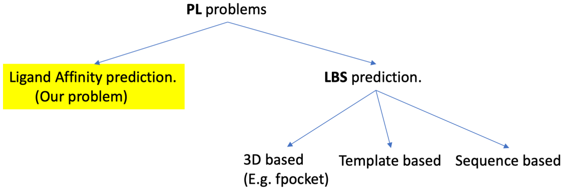
- Binding affinity between a protein and a ligand is quantified by the K_d, K_i and IC_{50}. Here K_d refers to the dissociation constant, K_i to inhibition constant, and IC_{50} to inhibitory concentration 50%.
- K_d can be quantified by using protein concentration $[P]$ and ligand concentration $[L]$ at equillibrium [1].

$$K_d = \frac{[P][L]}{[PL]}$$

- K_i and IC_{50} are similarly defined.

Problem Definition

- Determining if a potential drug (ligand) can bind to a target protein is very costly processes [3].
- The project aims to predict the ligand affinity based on previously recorded data (”In-Silico” method). This reduces the drug discovery costs.
- We use PDB databank, which holds PL affinity data collected over many decades.



PL problems

Ligand Affinity prediction.
(Our problem)

LBS prediction.

3D based
(E.g. fpocket)

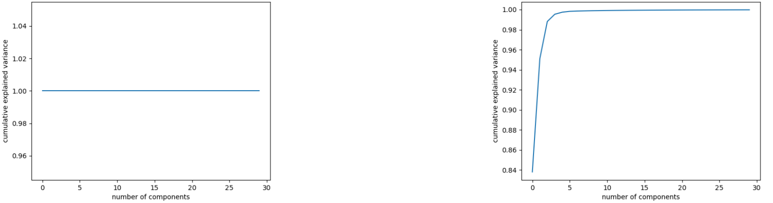
Template based

Sequence based

Figure: Protein-Ligand problem classifcation.

Data Preprocessing

- Anomalies such as NaN (Not a number) values were removed from the data before sending them as input to the model.
- We used PCA (principle component analysis) to find that the ligand feature *IPC* was having log scale values.



(a) With original Ligand feature IPC.

(b) With log scaled Ligand feature IPC.

Figure: Cumulative PCA of ligand features.

Feature Extraction

PDB databank (v2019) was used to extract input features.

- We use *fpocket/dpocket* ligand binding site prediction library to get the features of pockets pockets in proteins.
- *RDKit* library is used to extract features for each ligand.
- **Ligand Features:** Using *RDKit.Chem.Descriptors*, 402 features were extracted for each ligand. Hence the ligand features space was $\mathbf{R}^{402}$.
- **Protein Features:** For every pocket, 55 descriptors are obtained in total. Hence, the input space for protein features is $\mathbf{R}^{55}$

The concatinated input feature space before input feature elimination $\mathbf{R}^{457}$.

Feature Selection

We only had 16000 data points to train a feature space of $\mathbf{R}^{457}$. We reduced our features using the following feature selection strategies:

- **Output Correlation**: The input features that have the best *Pearson* and *Spearman* correlation were selected. [**?**].
- **Genetic Algorithms**: Genetic algorithms with the following score function was used to select the best features [4]:

$$\text{score} = \mathbf{R}^2\text{score} * \text{Features Eliminated}$$

- **Manual Feature Selection:** A selected list of 121 ligand descriptors was used with all protein descriptors as input to the model.

Dealing with measurement resolution

- In the PDB databank, each complex also has a corresponding measurement resolution.
- The structural detail of the 3D image is inversely proportional to the measurement resolution.
- The weighting of each data point was done according to hyperbolic formulae and linear formulae.

  $W_i = \frac{\max \mathrm{R}_{1\ldots\mathrm{n}}}{R_i}$; $W_i = (\max \mathrm{R}_{1\ldots\mathrm{n}} + 1) - R_i$

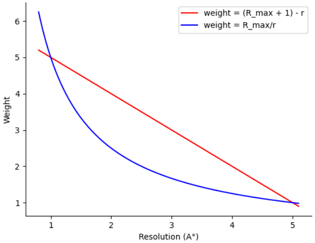


Figure: Weight calculation formulae.

Machine Learning models

Testing strategy

We use the following methods to determine the quality of results and reproducing them:

- **Reproducibility**: To reproduce the results, we use report random seed (Execution ID) for every execution.
- R^2 **score** (*Coefficient of determination*) [**?**]: . $R^2 \in (-\infty, 1.0]$ where 1.0 is the best score.
- **Visualization:** Our model's approximated function $f : \mathbf{R}^n \mapsto \mathbf{R}$ where $n \in \mathbf{I}^+$ is visualized as a 2D scatter plot.

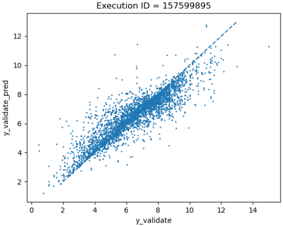


Figure: (Sample) Visualizing accuracy. $R^2 \approx 0.805$.

Results

The following are the results:

- 2,3,4
-

Discussion

The following points can be noted:

- Testing results were sometimes better than validation results.
-

Q & A

References

- Du, Li, Xia, Ai, Liang, Sang, Ji and Liu; Insights into Protein–Ligand Interactions: Mechanisms, Models, and Methods (2016)
- Le Guilloux, Schmidtke, and Tuffery; Fpocket: An open source platform for ligand pocket detection(2009)
- DiMasi, Grabowski and Hansen; nnovation in the pharmaceutical industry: New estimates of R & D costs (2016)
- John H. Holland. Genetic Algorithms. (1960)
- Is rotation forest the best classifier for problems with continuous features? A. Bagnall, M. Flynn, J. Large, J. Line, A. Bostrom, and G. Cawley (2020)