A METHOD AND SYSTEM FOR PREDICTING MUTATION-INDUCED BINDING AFFINITY CHANGES IN MEMBRANE PROTEIN COMPLEXES

IITM Technology Available for Licensing

Problem Statement

- **Membrane proteins** are key targets in **drug design**, influencing **therapeutic interventions** for diseases like cancer and cardiovascular conditions.
- Conventionally used **experimental methods** such as Surface Plasmon Resonance (SPR) and Isothermal Titration Calorimetry (ITC) are **resource-intensive** and **time-consuming.**
- Further, **computational methods**, while efficient, **lack specificity for membrane proteins**. Current **machine learning and deep learning methods** fail to specifically predict mutation-induced **binding affinity changes in membrane protein complexes**.
- There is a need for **an improved method to integrate structural and sequence-based features** with advanced models (e.g., Gradient Boosting Regressor (GBR)) for accurate, efficient binding affinity predictions.

Intellectual Property

- IITM IDF Ref 2979
- **IN 202441050394 Patent Application**

TRL (Technology Readiness Level)

TRL 4 Technology Validated in Lab

Technology Category/ Market

Category: Artificial Intelligence (AI) and Machine Learning/ Drugs and Pharmaceutical Engineering

Industry Classification:
Pharmaceutical and Drug Development; Biotechnology and Genetic Engineering

Applications:
Identifying the effects of mutations on membrane proteins; Critical to drug-target interactions; Precision Medicine and Personalized Healthcare; Study of disease pathogenesis; Structural Biology; Functional Analysis of Membrane Proteins; High-Throughput Screening and Computational Biology

Market report:
The global protein engineering market was valued at USD 4.35 billion in 2024 and is projected to grow to USD 20.86 billion by 2034 with a CAGR of 16.97%

Research Lab

Prof. Michael Gromiha M
Dept. of Biotechnology

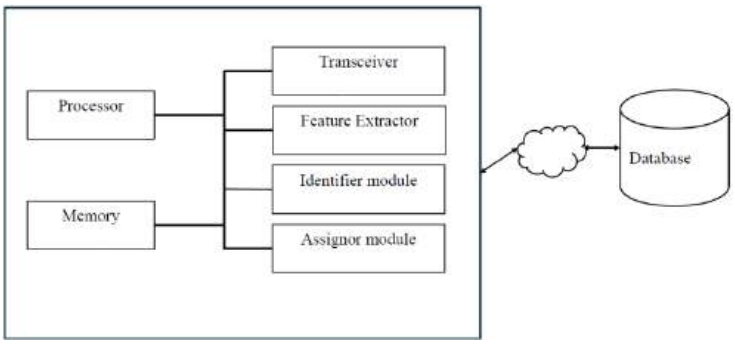

Figure: Illustrates an exemplary architecture of a system for predicting the change in binding affinity of the mutation-induced MP complex

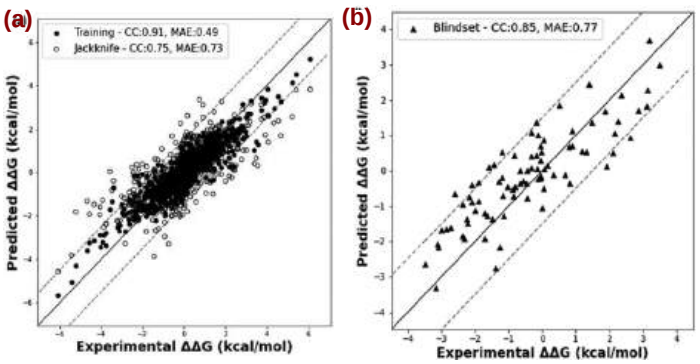

Figure: Scatter plots showing the relationship between experimental and predicted binding affinities on **(a)** training and jack-knife test and **(b)** the test set. The solid line represents ideal prediction and the dotted line shows the mutations predicted within ±1.5 kcal/mol deviation. For example, the mutation F269A in interferon lambda receptor 1 (IFNLR1) interacting with tyrosine- protein kinase JAK1 (PDB: 5IXD) resulted in a ΔΔG of 3.50 kcal/mol. The prediction the change in the binding affinity of the MP complex (3.98 kcal/mol) within a deviation of 0.48 kcal/mol is accurately predicted.

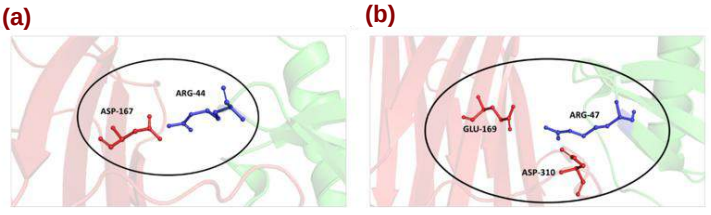

Figure: Structure of The SECRET domain (smallpox virus-encoded chemokine receptor) and its complex with chemokine CX3CL1 where **(a)** Arg 44 and **(b)** Arg 47 form electrostatic interactions in the interface. The experimental change in the binding affinity is 1.88 kcal/mol. The disclosed prediction process predicted the ΔΔG as 1.56 kcal/mol, indicating strong concordance with the experimental value.

CONTACT US
Dr. Dara Ajay, Head TTO
Technology Transfer Office,
IPM Cell- IC&SR, IIT Madras

IITM TTO Website:
https://ipm.icsr.in/ipm/

Email: headtto-icsr@icsrpis.iitm.ac.in
ttooffice@icsrpis.iitm.ac.in
Phone: +91-44-2257 9756/ 9845

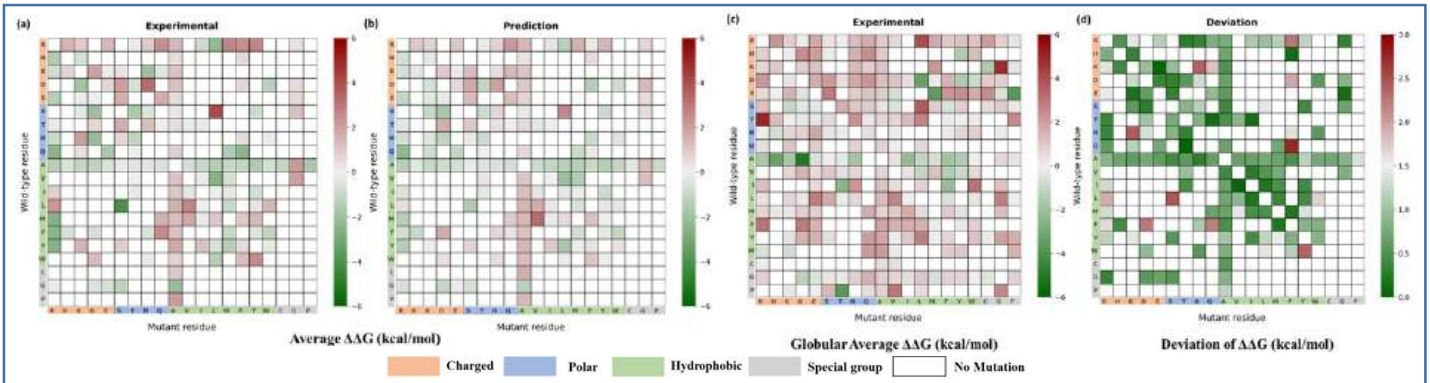

Figure: A comparative analysis of binding affinity changes upon mutation associated with different amino acid types. **(a)** and **(b)** are experimental and predicted average binding affinity changes upon mutation (kcal/mol) respectively, **(c)** is average ΔΔG for globular protein dataset, while **(d)** is the deviation between experimental and predicted ΔΔG (jack-knife test) upon each type of mutation (kcal/mol) in membrane protein complexes. Overall, comparing the patterns on the left and right panels, one can observe that the predicted patterns are remarkably similar to those of experimental data in terms of average binding energy changes. This consistency underscores the reliability and accuracy of the prediction model in capturing the change in binding affinity upon mutation.

Technology

The technology predicts mutation-induced binding affinity changes (ΔΔG) in membrane protein (MP) complexes, aiding in drug design, therapeutic interventions, and understanding mutation impacts on MP stability and interactions.

Utilizes structure-based (e.g., total energy, solvent accessibility) and sequence-based (e.g., physicochemical properties, conservation score) features. Employs forward feature selection for optimization, ensuring minimal multicollinearity and maximal relevance in predictions.

Achieves high prediction accuracy with Pearson correlation r=0.75, mean absolute error (MAE) =0.73 kcal/mol. Trained on a dataset of 770 MP mutations using Gradient Boosting Regressor and advanced bioinformatics tools.

Effective across MP functional classes (enzymes, receptors, transporters) and mutation types. Outperforms conventional methods (e.g., mCSM, SAAMBE) with reduced MAE and higher correlation, ensuring robust predictive performance.

Integrates a modular setup with processors, memory, and a database. Features extraction, feature selection, and prediction are automated for precise analysis, offering scalability for bioinformatics research and pharmaceutical applications.

Key Features / Value Proposition

- **Enhanced Feature Integration:** Combines structure-based features (e.g., total energy, inter-residue contacts) and sequence-based features (e.g., PSSM profiles, conservation score), unlike conventional methods that focus on limited aspects, ensuring a comprehensive analysis of mutation impacts.
- **Superior Prediction Accuracy**: Achieves Pearson correlation r=0.75 and MAE=0.73 kcal/mol, outperforming conventional methods (e.g., mCSM, SAAMBE) that show lower correlations and higher MAE (>1 kcal/mol).
- **Optimized Feature Selection:** Employs forward feature selection (FFS) to minimize multicollinearity and select the most relevant features, resulting in a more precise and computationally efficient prediction compared to exhaustive or manual feature selection methods.
- **Versatility Across Functional Classes:** Demonstrates robust performance across various MP functional classes (enzymes, receptors, transporters), with MAE ranging from 0.63 to 0.87, ensuring applicability to diverse biological systems.
- **Dataset and Methodological Superiority:** Trains on a high-quality dataset of single mutations with experimentally validated binding affinity data, leveraging Gradient Boosting Regressor (GBR) for capturing complex feature relationships, outperforming simpler regression models used in competing technologies.

CONTACT US
Dr. Dara Ajay, Head TTO
Technology Transfer Office,
IPM Cell- IC&SR, IIT Madras

IITM TTO Website:
https://ipm.icsr.in/ipm/

Email: headtto-icsr@icsrpis.iitm.ac.in
ttooffice@icsrpis.iitm.ac.in
Phone: +91-44-2257 9756/ 9845