Systematic evaluation of computational tools to identify potential drug-resistant mutations in the absence of experimental complexes

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Can we use AI programs to model protein structures and study the effect of mutations in drug resistance?

- **Drug resistance** caused by **mutations**, especially in many rapidly-evolved systems such as viruses and bacteria, raises significant global health concerns.

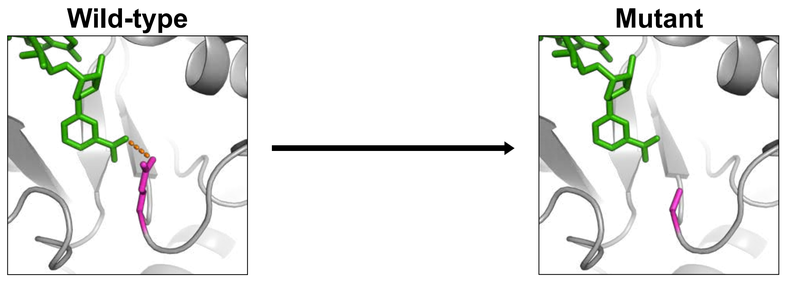

Fig 1. Effect of mutations on drug binding

- While many researchers incorporate **Artificial Intelligence (AI)** programs like **AlphaFold2** to study mutations and drug resistance, there is no systematic assessment on the methods to identify potential drug resistant mutations without using experimental structures.

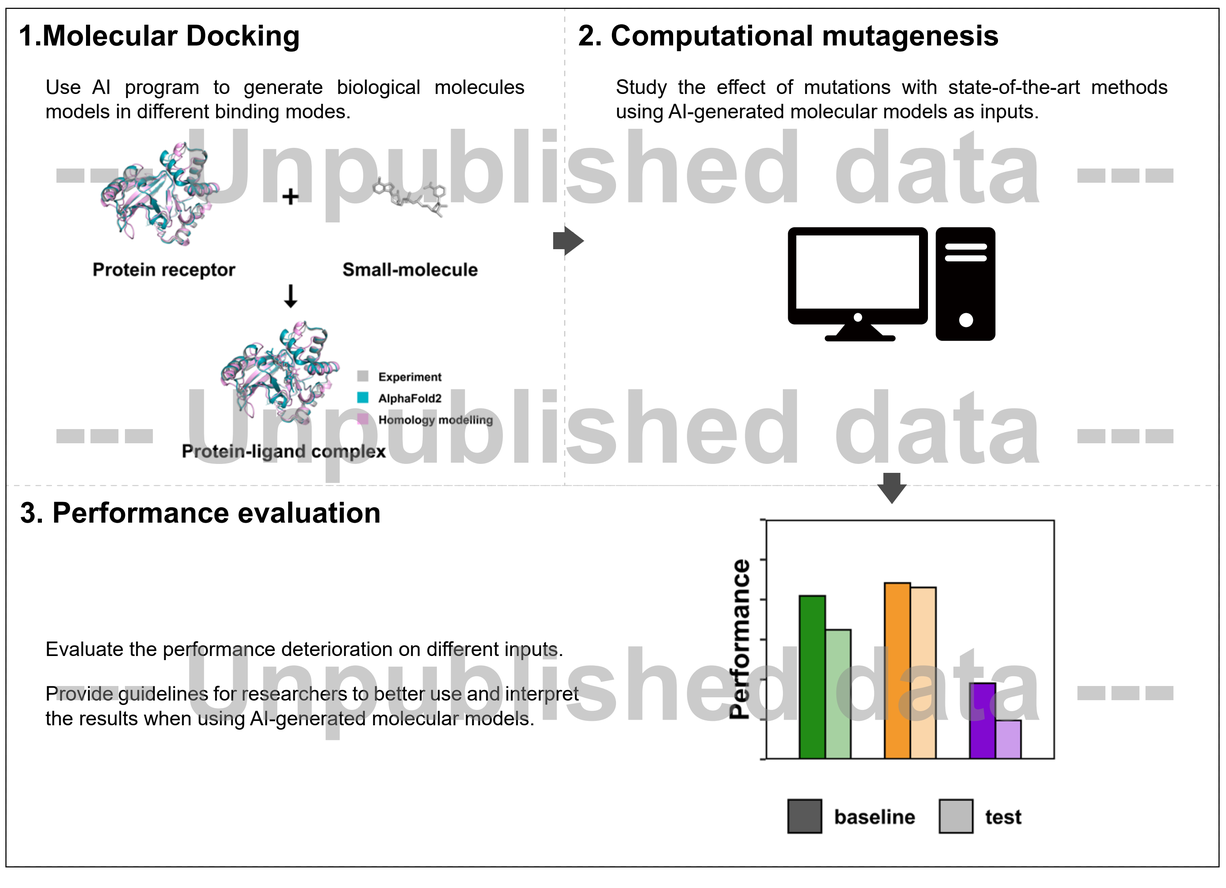

Fig 2. Methodology: research analysis workflow

Yes we can, but we need to pay attention to ...

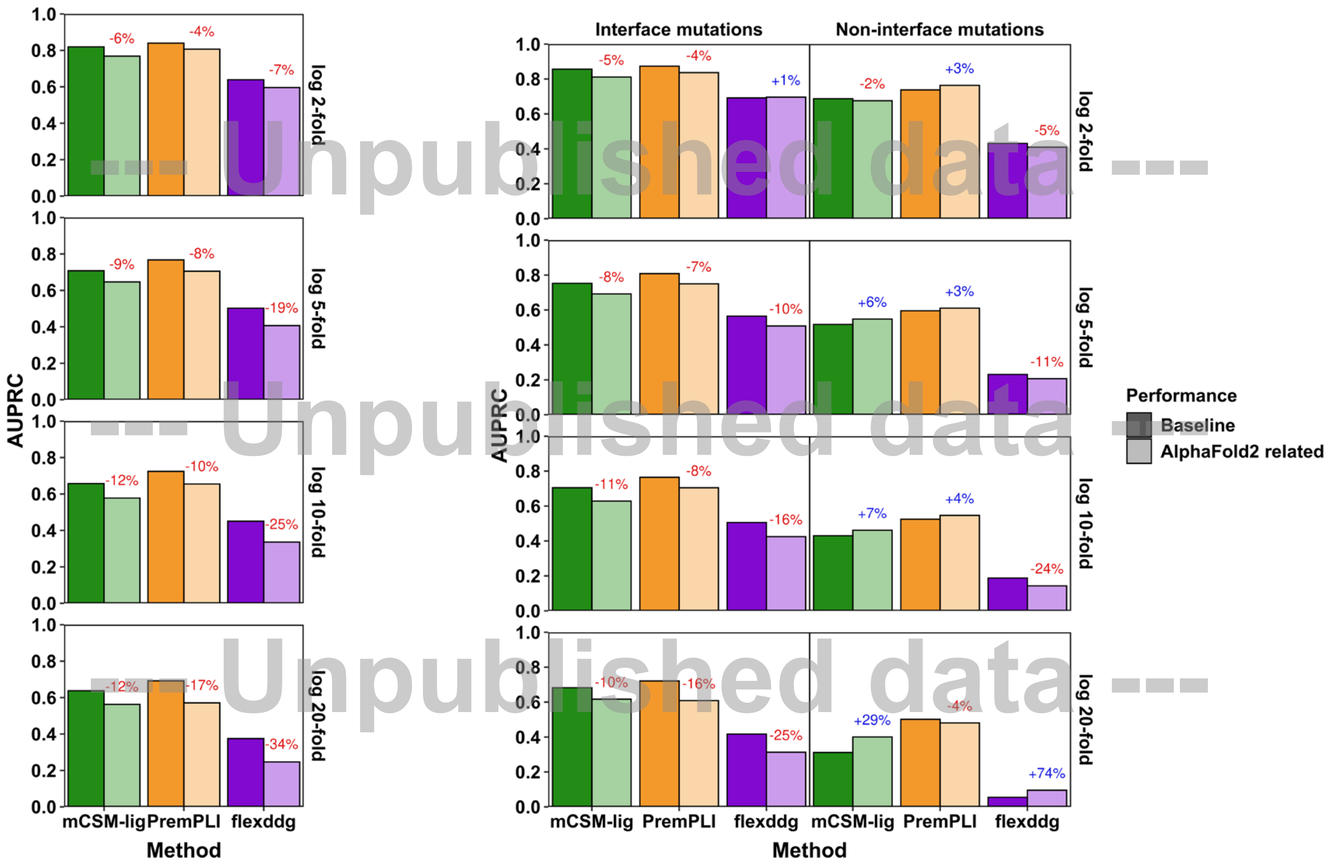

Fig 3. Predictive performance of methods to identify potential drug resistant mutations when taking AI-generated molecules as inputs.

- In this work, we observed that there is **~15% performance deterioration** for the current methods when using AlphaFold2-based molecules as inputs to identify potential drug-resistant mutations.
- This consistent performance deterioration could also be observed in different biochemical properties of receptors, such as **interface mutations**.

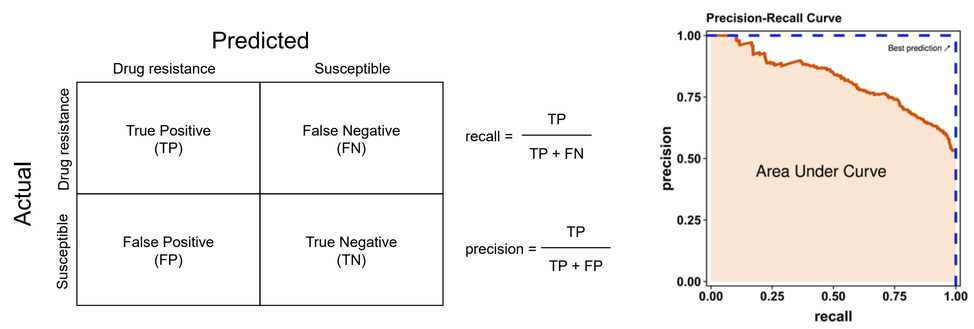

Fig 4. Area Under Precision-Recall Curve (AUPRC)

Potential application

- This work could provide **fundamental guidelines** for better interpretation on the predictions of current methods when using AI-generated protein-ligand complexes as inputs to characterise potential drug-resistant mutations
- Our study may provide new insights to improve drug efficacy and stewardship.

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Digitial poster

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