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

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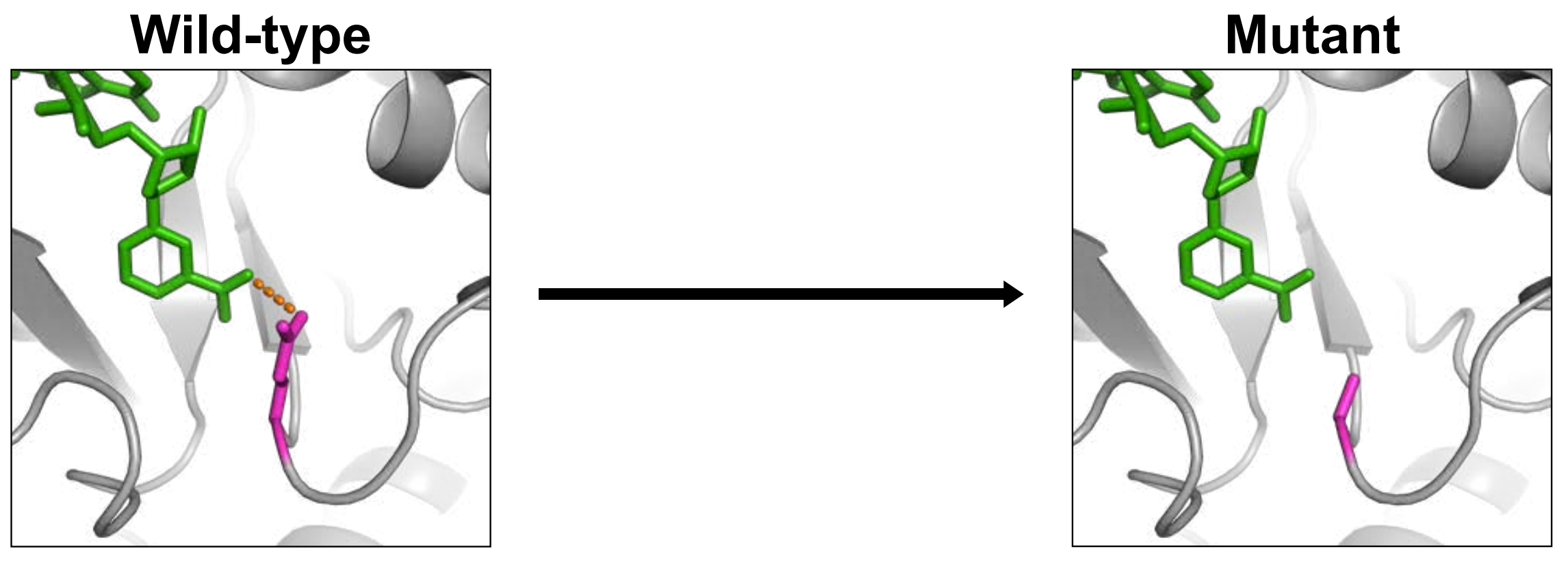
Can we use AI programs to model protein structures and study the effect of mutations in drug resistance?

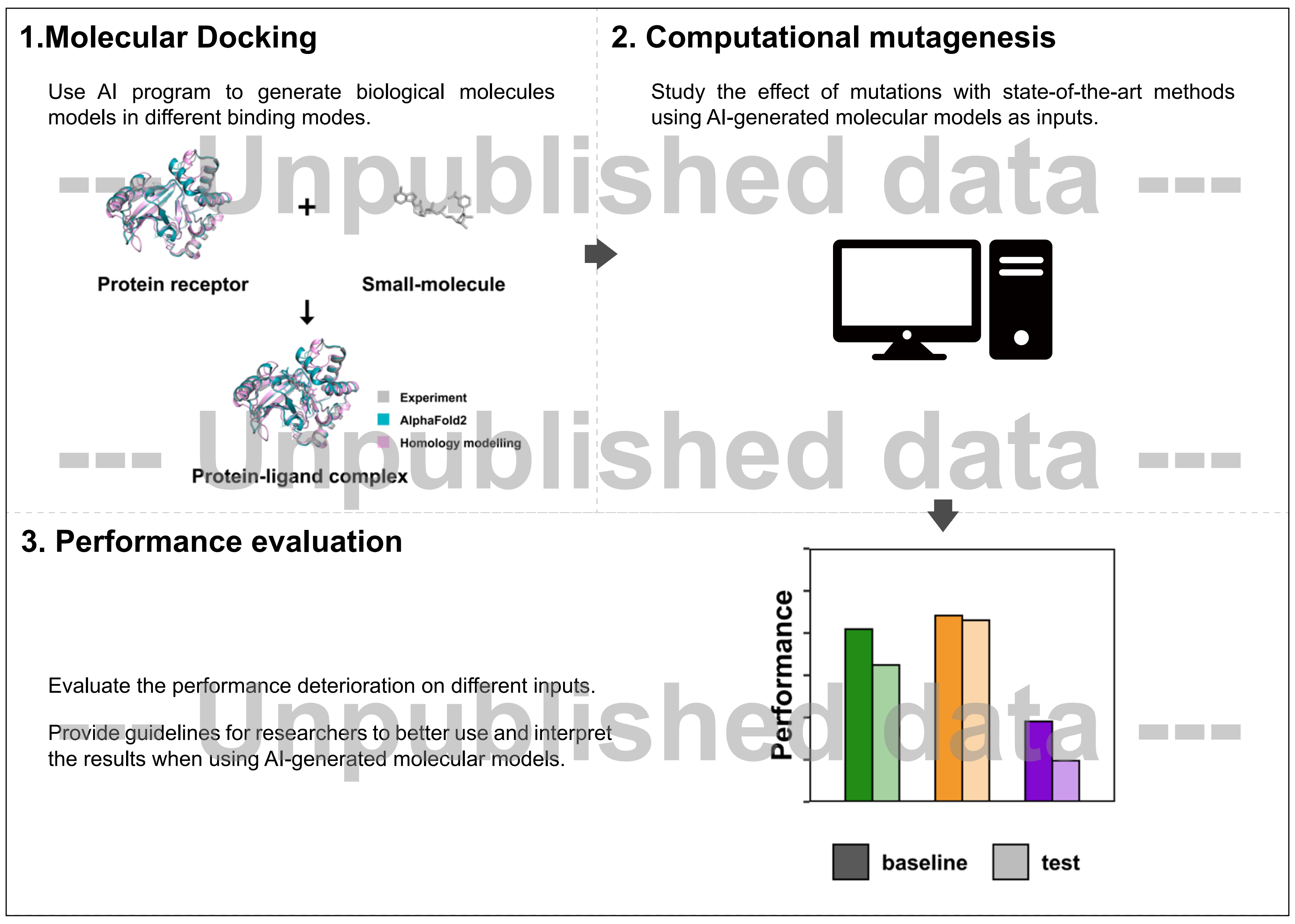
- **Drug resistance** caused by **mutations**, especially in many rapidly-evolved systems such as viruses and bacteria, raises significant global health concerns.



$$\Delta\Delta G_{bind} = \Delta G^{wt}_{bind} - \Delta G^{mt}_{bind}$$

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.



1.Molecular Docking

Use AI program to generate biological molecules models in different binding modes.

2. Computational mutagenesis

Study the effect of mutations with state-of-the-art methods using AI-generated molecular models as inputs.

3. Performance evaluation

Evaluate the performance deterioration on different inputs.

Provide guidelines for researchers to better use and interpret the results when using AI-generated molecular models.

Fig 2. Methodology: research analysis workflow

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

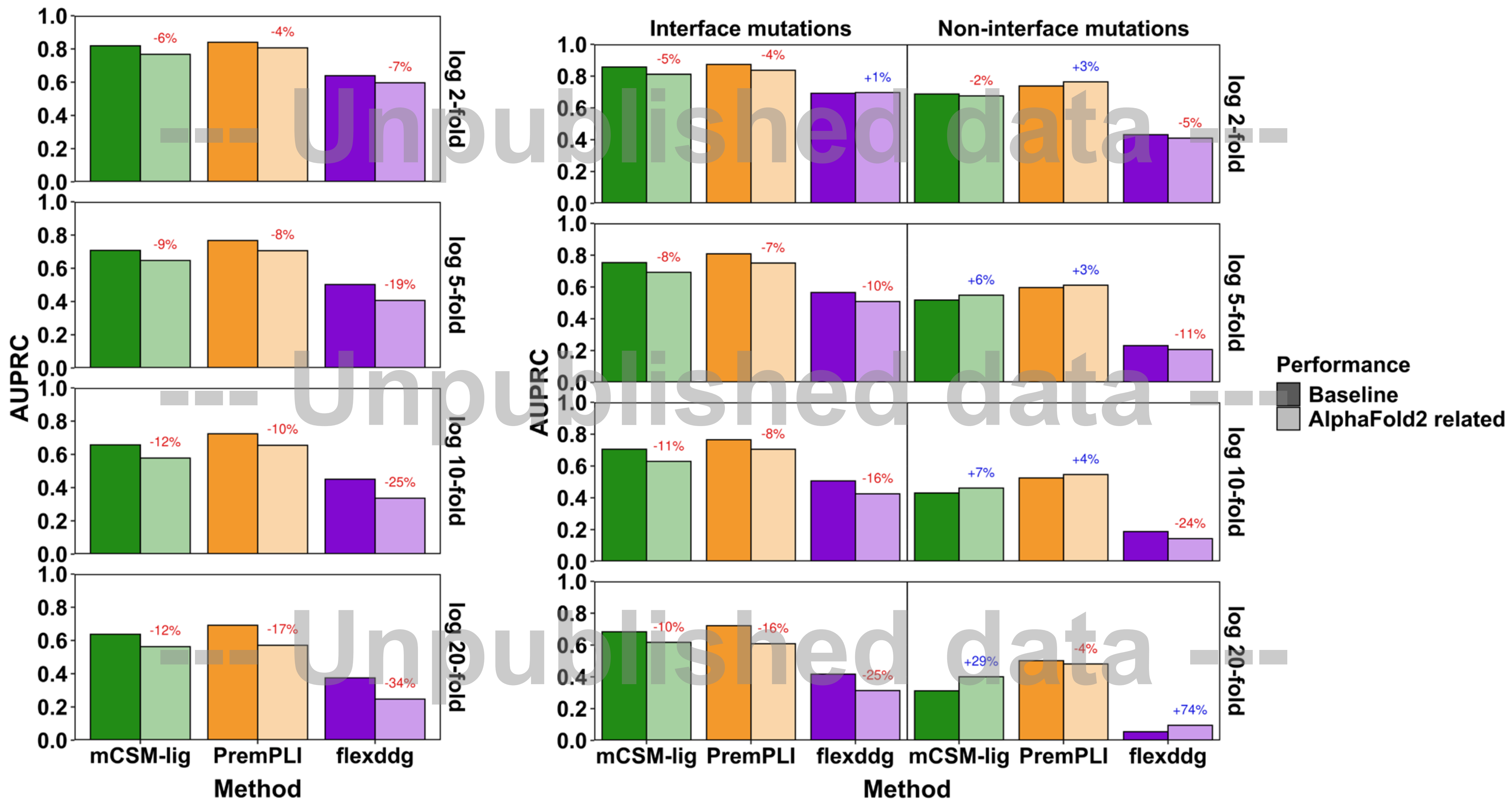


Fig 3. Predictive performance of methods to identify potential drug resistant mutations when taking AI-generated molecules as inputs.

- 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**.

Predicted

Actual	Drug resistance	Susceptible
Drug resistance	True Positive (TP)	False Negative (FN)
Susceptible	False Positive (FP)	True Negative (TN)

$$\text{recall} = \frac{TP}{TP + FN}$$

$$\text{precision} = \frac{TP}{TP + FP}$$

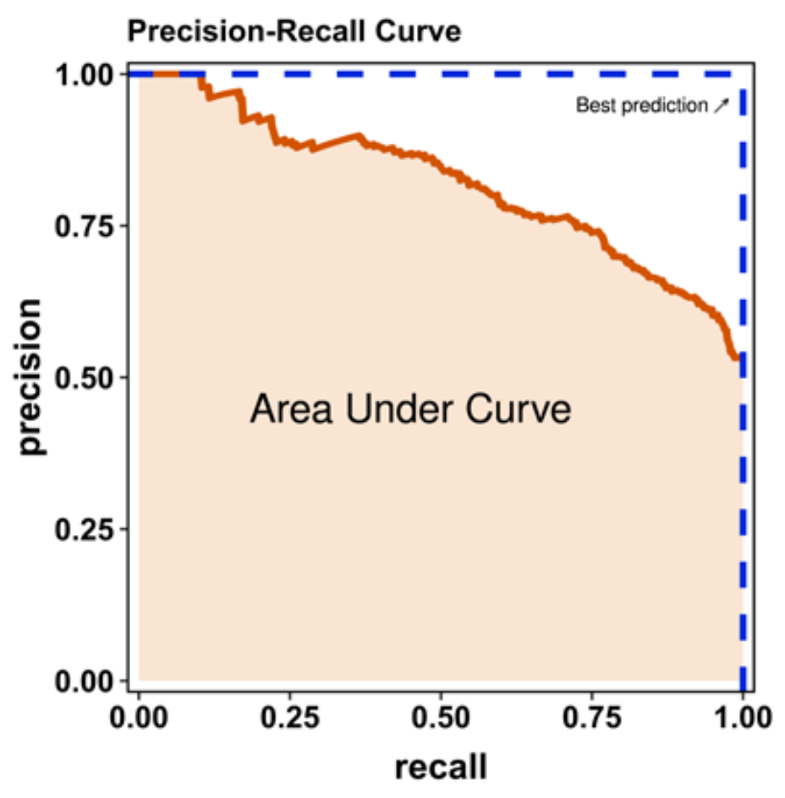


Fig 4. Area Under Precision-Recall Curve (AUPRC)

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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