Peptide-Protein Complex Structure Prediction Using Template Structures Generated by Docking Software in AlphaFold2

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Study 1 : Generating accurate structure with Template-Guided AlphaFold2

Purpose : To guide AlphaFold to generate structures more consistent with experimental results

Method : Docking simulation results were used as structural templates for AlphaFold predictions

Results : This approach produced more accurate peptide–protein complex structures than the original AF2-Multimer

Study 2 : Identifying the Correct Model via Interaction Residue Prediction

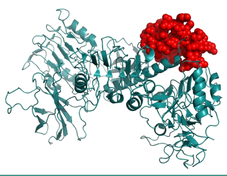
Purpose : To identify the correct structure among multiple predicted structure

Method : A protein language model was fine-tuned to predict interaction residues from sequence information, and these predictions were used to evaluate generated structures

Results : The predicted interaction residues enabled more reliable structure selection from multiple candidates

Introduction Better AlphaFold predictions of peptide–protein complexes are needed

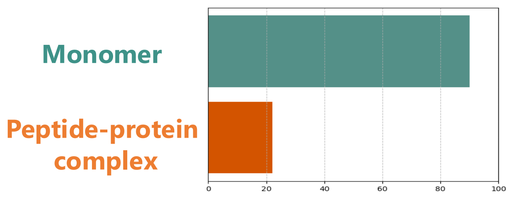
It is estimated that 15–40% of protein–protein interactions are mediated by peptides

(Ex.) 

Insulin

This peptide-protein interaction stops glycogen Breakdown and lowers blood glucose levels

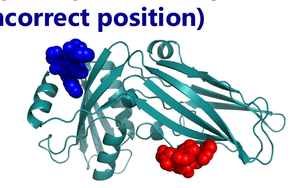
The success rates of structure prediction by AlphaFold



approximately 90%
Callaway, *Nature* (2020)

approximately 22% (AF2-Multimer)
Johansson-Åkhe, *Front. Bioinform* (2022)

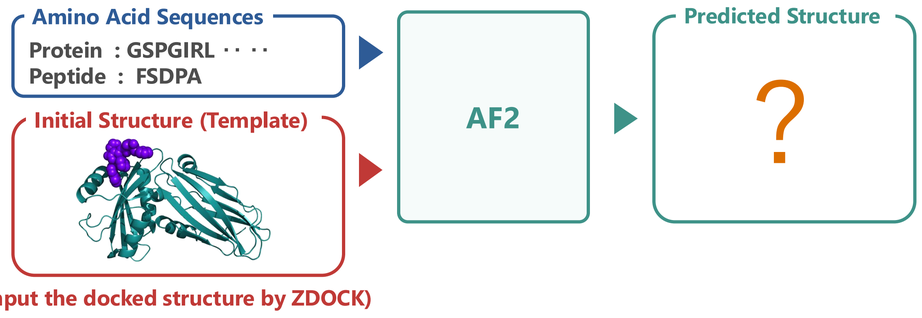
Peptide predicted by AF2-Multimer (Incorrect position)



Peptide in experimental structure (Correct position)

Study 1 Generating Accurate Structure with Template-Guided AlphaFold2

Method Use docking simulation results as structural templates for AF2 prediction



(Input the docked structure by ZDOCK)

We tested 18 complexes that original AF2-Multimer could not predict well (DockQ < 0.49)

ZDOCK : Software for docking peptide and protein

Rong Chen *et al*, *Proteins: Structure, Function, and Bioinformatics (2003)*

Protein and peptide are treated as rigid bodies

Outputs a structure combining one peptide and one protein

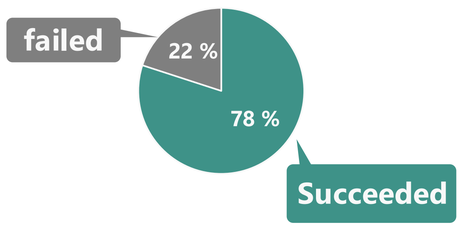
Places the peptide in various positions around the protein based on an energy function

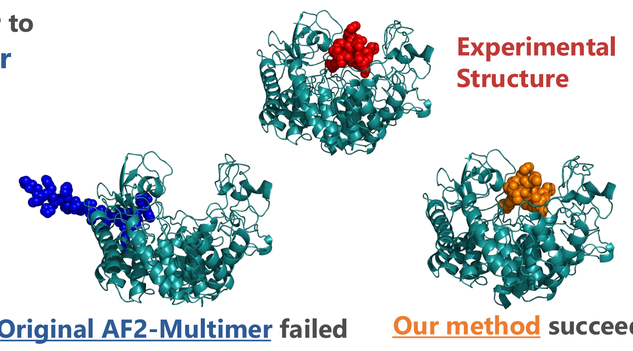
- Shape Complementarity
- Electrostatic interaction
- Desolvation Energy

structure outputted by ZDOCK
(100 structures are superimposed out of a total of 2000)

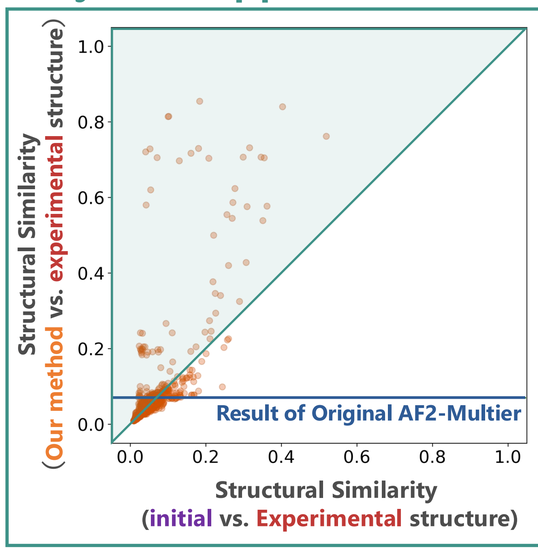
Result Providing an initial structure produced more accurate results than standard AlphaFold2

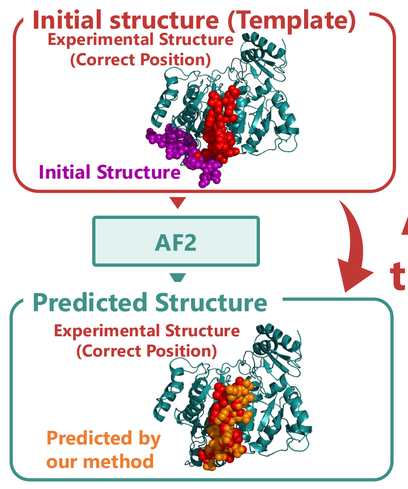
Our method succeeded to generated results closer to the correct structures than original AF2-Multimer in 78% (14 out of 18 types) of the complexes.





Why this approach works well?



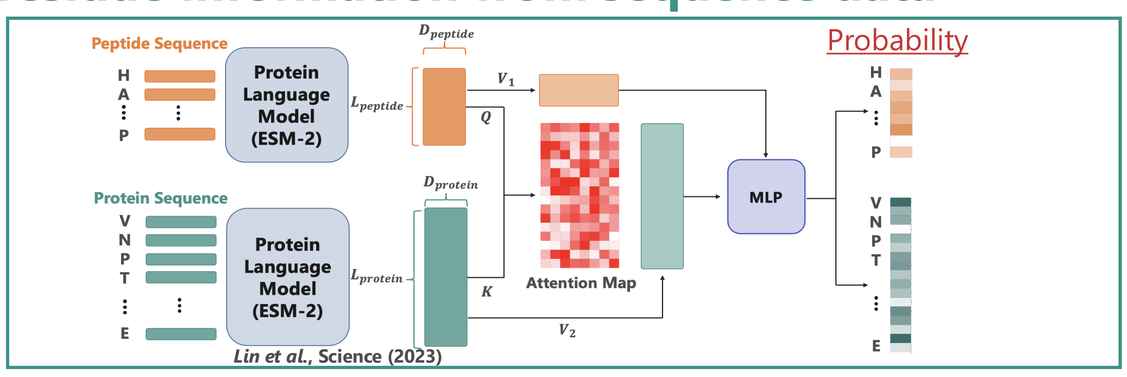


AF2 can refine the initial structure

(※One example out of 14 types)

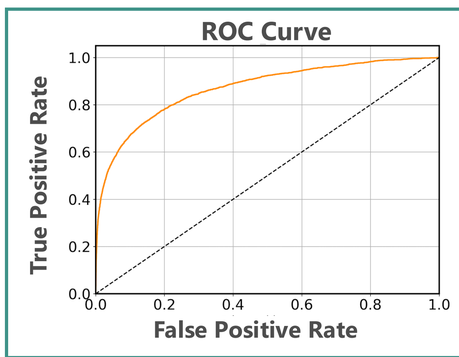
Study 2 Identifying the Correct Model via Interaction Residue Prediction

Method Fine-tuning a PLM to extract interaction residue information from sequence data



Lin et al., Science (2023)

Result 1 Fine-tuned PLM can predict interaction residues accurately



The model achieved an AUC of 0.87 on the test set, demonstrating good predictive performance

Result 2 Removing non-interacting predictions helped clarify the selection of the correct structure

Excluding predicted structures lacking interactions between high-probability residues, top-5 selected predictions exceeded the baseline in 33% (6 out of 18) of the complexes