

論文 / 著書情報
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論文要旨

THESIS SUMMARY

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要旨 (英文 800 語程度)

Thesis Summary (approx.800 English Words)

Drug discovery targeting protein-protein interactions (PPIs) has attracted much attention and has potential applications in several disease areas. Various modalities have been explored in PPI drug discovery. The physicochemical properties of the broad and shallow PPI interface are different from those of a typical ligand pocket, making it difficult to design effective PPI drugs with small molecule compounds. In addition, antibodies cannot target intracellular proteins, cannot be orally administered, and are moreover more costly to manufacture. Therefore, peptides are attracting attention as a PPI targeting modality as molecules that have properties of both small molecules and antibodies. The peptides are composed of 20 amino acids and have the advantage of binding to broad and shallow PPI interface. Peptides have also been developed that have various physical properties that allow them to permeate cell membranes. Peptides are easily degraded by digestive enzymes, but attempts are being made to improve their bio-stability by cyclization. On the other hand, there are several challenges in designing peptides computationally. The more residues a peptide has, the wider the search range becomes and the more difficult it is to search for all peptide sequences. In addition, peptides are flexible molecules, and so far, accurate prediction of their structure and affinity prediction by calculating their energy scores have not been developed. The high computational cost of using physicochemical energy calculations based on molecular simulations has been a necessary challenge. As a result, efficient exploration of peptide sequences is a difficult task. Although physical properties such as solubility and membrane permeability need to be considered for drug-discovery molecules, it is also difficult to incorporate these properties in conventional peptide design methods. While cyclic peptides are superior in terms of metabolism and stability, predicting the complex structure of cyclic peptides with target proteins has been considered challenging, which complicates computational design.

To address the challenges of peptide design, with a focus on optimization of physical properties and structural diversity, an approach combining protein structure prediction methods and deep network hallucination was employed in this study. Among the optimization of physical properties, solubility was selected as an example. In addition, it focuses on expanding the scope of application to cyclic peptides, which could not be addressed by the peptide design method based on protein structure prediction methods.

First, this study focused on linear peptides. Using the deep network hallucination method, which relies solely on the loss function that utilizes AlphaFold's output, a trend was observed where peptide sequences with high binding abilities exhibited poor solubility, posing challenges for sequence design. To ensure solubility, this study proposed a sequence design method that optimizes both solubility and binding ability by designing a loss function that utilizes not only AlphaFold's output but also the physical property index values of the amino acid residues used in the sequence. As a result, it became possible to design sequences that can be expected to bind while maintaining solubility. The designed peptides were evaluated for their solubility and estimated binding energy and compared with native peptides. In the design for the MDM2/p53 target, actual improvements in solubility and decreases in estimated binding energy were confirmed. In particular, compared to PDIQ, which has the highest binding ability to MDM2, successful design of peptide sequences with good computational binding free energy values was achieved.

The designed sequences tend to be very similar to the native p53 sequence with regards to the amino acid residues interacting with the MDM2 hotspot. The other amino acid residues tend to be composed of hydrophilic residues, which allowed for the design of sequences with high solubility, despite

having low estimated binding energy.

In addition, this study also made it possible to handle cyclic peptides. Inspired by Rettie's method of cyclizing the N-ter and C-ter of AlphaFold's input sequence, an approach was implemented to enable the prediction of protein-cyclic peptide complex structures using AlphaFold. This allowed for high-precision protein-cyclic peptide complex structure prediction. Furthermore, the deep network hallucination method was implemented to design cyclic peptide sequences that can be expected to have target binding ability, just like linear peptides. Successful design of cyclic peptides for some protein-peptide complexes, including the MDM2/p53 target, and the PD1/PD-L1 target, which is a protein-peptide complex were achieved.

In conclusion, this study has made progress in the field of peptide design for PPIs. The method developed in this research achieves simultaneous optimization of solubility and estimated binding energy, and also enables the design of cyclic peptides. Furthermore, it demonstrates the potential of deep network hallucination based methods in protein design, offering promising directions for future research in this field.

備考：論文要旨は、和文 2000 字と英文 300 語を 1 部ずつ提出するか、もしくは英文 800 語を 1 部提出してください。

Note : Thesis Summary should be submitted in either a copy of 2000 Japanese Characters and 300 Words (English) or 1copy of 800 Words (English).

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