Peptide Design using PepIT and Enhanced by AI-Based Tools

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Disrupting protein-protein interactions (PPIs) involved in disease is difficult with small molecules due to the large contact area of the PPI (approximately 1,000-4,000 Å^2) and the lack of well-defined pockets. Compared to small molecules, peptides have a broader and flatter interaction interface that is adapted to IPP interactions. In addition, peptide drugs offer superior stability, high purity and lower production costs [1].

The search for interesting peptides or the improvement of existing peptides can be performed experimentally by biophysical approaches such as site-directed mutagenesis, by peptide shuffling or phage display techniques. However, all these experimental approaches can be time-consuming and costly.

To design a therapeutic peptide able to specifically inhibit a PPI, we developed a new computational approach called PepIT [2]. PepIT is an R package that implements a strategy based on binding site comparison. The method is intended to be a fast approach, usable on a large peptide bank, which could provide a pre-screening of peptide libraries.

Recent advances in deep learning and generative artificial intelligence (AI) have significantly impact-ed complex modeling and peptide design. In particular, generative AI-based methods, such as RFdif-fusion [3] or BoltzGen [4] have significantly simplified and enhanced peptide design. Diffusion modeling generates protein backbones without relying on pre-existing designs and allows the design of peptides that bind to disease-associated proteins using only the structure or sequence of the target.

We have assessed several generative tools and our results suggest that the estimated binding affini-ties of the peptides retrieved by PepIT are improved by an optimization step performed using OpenMM [5], ProteinMPNN [6] and Boltz-2 [7], showing a significant improvement compared to AI-based peptide generation alone.

For one protein target, the PepIT pipeline identified 1,400 diverse peptides. In a peptide array exper-iment conducted in collaboration with experimental partners, 10 peptides were identified as strong binders. These results demonstrate that PepIT is competitive with the recently developed program BoltzGen.

Bibliography:

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