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Protein–peptide docking: opportunities and challenges

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Highlights:

- We provide an overview of protein-peptide docking methods and their applications
- Peptide docking tools can be divided on template-based, local and global methods
- Challenges in peptide docking include: sampling, scoring and integrative modeling
- Peptide docking tools offer a number of opportunities in structure-based drug design

Abstract

Peptides have recently attracted much attention as promising drug candidates. Rational design of peptide-derived therapeutics usually requires structural characterization of the underlying protein–peptide interaction. Given that experimental characterization can be difficult, reliable computational tools are needed. In recent years, a variety of approaches have been developed for 'protein–peptide docking', that is, predicting the structure of the protein–peptide complex, starting from the protein structure and the peptide sequence, including variable degrees of information about the peptide binding site and/or conformation. In this review, we provide an overview of protein–peptide docking methods and outline their capabilities, limitations, and applications in structure-based drug design. Key challenges are also briefly discussed, such as modeling of large-scale conformational changes upon binding, scoring of predicted models, and optimal inclusion of varied types of experimental data and theoretical predictions into an integrative modeling process.

Keywords: molecular docking; protein–peptide interactions; protein interactions; molecular modeling; structure-based drug design; structural bioinformatics; protein–peptide complex; peptide design; peptide therapeutics; peptide drugs.
Teaser: A variety of methods have been developed for the molecular docking of peptides to proteins. In this review, we provide an overview of protein–peptide docking tools and outline their capabilities, limitations, and applications in structure-based drug design.

Introduction

Computational docking methods have proven to be useful in the discovery and design of small-molecule drugs. Similar efforts are being made in the field of peptide therapeutics [1,2]. However, the docking methods designed for small-molecule interactions are usually not well suited for the modeling of the significantly more flexible and larger peptide molecules [3]. The interest in peptide therapeutics [4,5] triggered the rapid development of new techniques dedicated to protein–peptide docking [1,2], which are being increasingly incorporated into the drug discovery and design process [6–18]. In this review, we outline state-of-the-art protein–peptide docking methods. We first provide an overview of the available software solutions and discuss the opportunities they offer and then highlight the main challenges in the field of protein–peptide docking.