Protein–peptide docking: opportunities and challenges

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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.

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.

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Different methods–different opportunities

Protein–peptide docking methods can be divided into three categories: template-based docking; local docking; and global docking (Fig. 1). Different approaches offer different levels of prediction accuracy, often determined by the amount of interaction information provided as input. A summary of the main currently available tools and servers is presented in Table 1.

Template-based docking

Template-based (comparative) docking methods use known structures (templates) as scaffolds to build a model of the complex [19–21]. One of the most common docking practices is to thread receptor and/or peptide sequences through a template structure. This method can be particularly effective if the template is similar to the investigated complex [22,23]. Template-based docking is usually performed manually or semiautomatically using a set of tools for sequence–structure comparison and analysis. The GalaxyPepDock [19] web server

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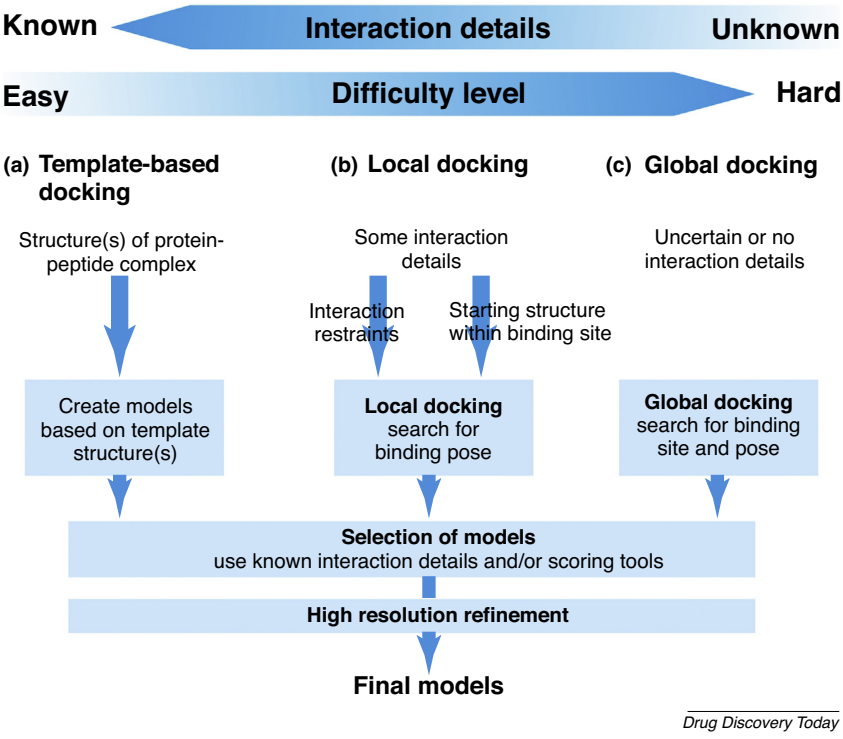

FIGURE 1

Typical pipelines for protein–peptide molecular docking. Docking methods can be divided into three categories according to the amount of required input data: (a) template-based methods that utilize knowledge about the structure of similar complexes (templates); (b) local docking methods that require some knowledge about the binding site; and (c) global docking methods that assume no knowledge about the peptide beyond its sequence.

provides a fully automated template-based approach. It searches for templates based on similarities of the input protein structure and protein–peptide interaction to structures of complexes stored in PDB. Next, it builds complex models using energy-based optimization and refinement that allows for structural flexibility. Template-based docking of highly homologous complexes is also provided by protocols dedicated to the prediction and design of peptide binding specificity [15]. For example, the FlexPepBind protocol enables the modeling of different peptide sequences into a receptor binding site, with constraints that reinforce defined critical features, such as conserved hydrogen bonds [15]. Additionally, template-based modeling methods can also use fragments of monomeric proteins [24,25] and interfaces from protein–protein complexes to build modeling scaffolds [3,26]. Structures of protein–protein interaction interfaces are particularly useful in the design of peptide inhibitors of protein–protein interactions [1,3,26].

Local docking

Local docking methods perform a search for a peptide binding pose in the proximity of a user-defined binding site; therefore, docking accuracy depends on the input information on the binding site: the more precise, the better. The available methods use different ways of defining the binding site. Rosetta FlexPepDock [27], DynaDock [28], or PepCrawler [29] require an initial model of the complex prepared by the user. As demonstrated, the methods should enable improvement of the initial model if its accuracy is in the range of approximately 5 Å backbone- root-mean-square deviation (RMSD) from the experimental structure. Additionally, the input model may need some method-specific preparation, such as elimination of internal clashes [15]. However, some of the methods require less rigorously defined initial models. For example, the input peptide conformation in Rosetta FlexPepDock *ab initio* [30] might be far from the native, because the method enables high flexibility of the peptide and extensive sampling of rigid body orientations within the binding site. By contrast, HADDOCK [31] can automatically place the peptide in the proximity of the binding site defined by a user-provided list of interface residues [32]. Another group of local docking methods comprises tools dedicated to small-molecule docking. The applicability of these methods (AutoDock Vina [33], Gold [34] or Surflex-Dock [35]) is limited to short peptides (up to a few amino acids). They also require the user to manually place a peptide conformation within the binding site. All three methods were validated against an up-to-date benchmark of protein–peptide complexes and produced near-native models in 19%, 30%, and 38% of cases, respectively [36]. As presented recently, the peptide size limitation of small-molecule docking tools could be overcome by docking peptide fragments [37,38] (see the DINC 2.0 web server [37] in Table 1). Finally, local docking methods can be used for refining medium-quality models to better resolution (e.g., the PIPER-FlexPepDock [39] global docking protocol successfully uses Rosetta FlexPepDock [27] for the refinement of top-scored models): if Rosetta FlexPepDock is provided with a high-quality initial model, it can yield even subangstrom resolution [11,15].

Global docking

Global docking methods perform a coupled search for the peptide binding site and pose. The simplest approach to global protein–

TABLE 1

Overview of protein–peptide docking approaches

Method	Server	Required input[a]	Description	Performance[b] on benchmark sets and comments	Refs
GalaxyPepDock	http://galaxy.seoklab.org/pepdock and a standalone version	N/A	Template-based docking procedure: (i) search for templates based on structure and interaction similarity; (ii) model building by energy-based optimization; (iii) energy-based scoring; and (iv) refinement of final structures	Tested on unbound complexes from PeptiDB [45] database: medium resolution or better models obtained; used in study to design peptide ligands for neuronal polo-like kinase [10], where it was used to redock fragments extracted from protein–protein interfaces	[19]
PepComposer	http://biocomputing.it/pepcomposer/webserver	B (does not require peptide sequence)	Template-based docking procedure: (i) search for regions structurally similar to region of predefined binding site in database of experimentally solved monomeric proteins; (ii) retrieve continuous backbone fragments in contact with region of binding site; and (iii) design peptide sequence	Tested on LEADS-PEP [36] set: in ~50% of cases (23 out of 53), median backbone RMSD between designed peptide ranking first and native peptide was 1.9 Å (or 1.1 Å if best out of first ten-ranked peptides was considered, accounting for 25 out of 53 cases); direct comparison with other tools is not straightforward, because Pepcomposer does not use sequence of docked peptide and designed peptides are usually shorter than native ones [24]	[24]
Rosetta FlexPepDock	http://flexpepdock.furmanlab.cs.huji.ac.il and standalone version	PcB	Local docking procedure: Monte Carlo-based optimization of fully flexible peptide within binding pocket. Receptor flexibility limited to side-chains, but can be extended to full receptor. Clustering and scoring according to Rosetta energy function	Tested on locally perturbed complexes from PeptiDB [45]: near-native or better models obtained for input structures perturbed up to 5–6 Å peptide RMSD from native [27]; *ab initio* FlexPepDock version [30] enables extensive sampling of peptide backbone conformations. FlexPepBind extension [15] enables prediction of relative binding affinities for given receptor; in drug design studies, often used for high-resolution refinement of models to recover atomistic details of interaction [10,12]; e.g., successfully used to find binding modes of peptide inhibitor of *Pseudomonas aeruginosa* MurA enzyme [6] and to investigate unknown binding mechanism of ALOS4 to integrin in development of a non-RGD cyclic peptide drug conjugate for human metastatic melanoma treatment [9]; performs well for pHLA complexes [11] and peptide–MHC complexes [16]; also used as a part of ToxDock tool, dedicated to prediction of binding modes of peptide toxins to ion channels [18]	[27]
DynaDock	Not available publicly	PcB	Local docking procedure: (i) rigid-body optimization of peptide orientation within binding site, followed by (ii) refinement of fully flexible peptide receptor with Optimized Potential Molecular Dynamics procedure (using soft-core potentials for implicit receptor flexibility)	Tested on custom set of locally perturbed bound (15) and unbound (4) cases: near-native or better models obtained in most bound cases; performed best for input peptide conformations within 5.5 Å peptide RMSD from native	[28]
PepCrawler	http://bioinfo3d.cs.tau.ac.il/PepCrawler/	PcB	Local docking procedure: (i) fully flexible peptide docked with Rapidly-exploring Random Trees algorithm, followed by (ii) clustering-based scoring. Receptor flexibility limited to side-chains	Tested on set of 25 complexes from PeptiDB [45] combined with 18 additional complexes: near-native or better models obtained in most cases; performed best for input peptide conformations within 5 Å backbone RMSD from native	[29]
HADDOCK peptide docking	http://milou.science.uu.nl/services/HADDOCK2.2/haddock.php	PcB (user lists binding site residues)	Local docking procedure: (i) generation of peptide structures by threading peptide sequence onto three peptide conformations (alpha-helix, polyproline-II or extended); (ii) rigid-body docking of peptide structures within binding pocket; (iii) scoring based on binding free energy (calculated using dampened Molecular Mechanics Poisson–Boltzmann Surface Area); (iv) flexible refinement of model; peptide and interacting residues of receptor are fully flexible	Tested on PeptiDB [45] database: near-native or better models obtained; enables incorporation of sparse experimental data to guide docking [62]; successfully used to perform high-throughput docking [14] and to incorporate NMR data into drug design process [13]	[31]
PEP-FOLD 3	http://bioserv.rpbs.univ-paris-diderot.fr/services/PEP-FOLD3	PcB[a]	Local docking procedure: (i) generation of starting poses; (ii) Monte-Carlo-based sampling of peptide conformation; (iii) RMSD-based clustering of resulting models	Tested on PeptiDB [45] database: medium–high-quality models obtained; provides framework for structural characterization of peptides both in solution and in complex with protein	[68]

TABLE 1 (*Continued*)

Method	Server	Required input[a]	Description	Performance[b] on benchmark sets and comments	Refs
AutoDock Vina	Standalone version	Pc and B (user marks binding region)	Local docking procedure: Monte-Carlo-based sampling of peptide conformations within binding pocket. Receptor flexibility is by default limited to side-chains, but can be extended to include backbone	Tested on LEADS-PEP [36] set and on a custom set of 47 complexes: medium-resolution models obtained [36]; performed best for short peptides (up to four residues) [33]; standard docking tool for small-molecule ligands; has been used to perform high-throughput docking [12] and to design protein–protein interaction inhibitors [17]	[33]
DINC 2.0	http://dinc.kavrakilab.org	Pc and B (user marks binding region)	Local docking procedure: based on AutoDock 4 for docking long peptides, in which peptide is divided into segments of increasing length. During docking, receptor structure remains rigid	Tested on custom set of 73 complexes from PDB. More accurate and faster than standard protocol recommended for docking large ligands using AutoDock (Dinc version 1.0); improved version (Dinc 2.0) enables docking of more challenging peptides (e.g., >25 flexible bonds)	[37]
Gold	Standalone version	Pc and B (user marks binding region)	Local docking procedure: Monte-Carlo-based sampling of peptide conformations within binding pocket. Receptor flexibility either limited to side-chains or implicit (ensemble docking)	Tested on LEADS-PEP [36] set: medium-resolution models obtained [36]; standard docking tool for small-molecule ligands; used in drug design study to identify best MHC binder peptide [8]	[34]
Surflex-Dock	Standalone version	Pc and B (user marks binding region)	Local docking procedure: rotamer library-based generation of peptide conformations within binding pocket. Receptor flexibility limited to binding pocket	Tested on LEADS-PEP [36] set: medium-resolution models obtained [36]; standard docking tool for small-molecule ligands	[35]
pepATTRACT	http://bioserv.rpbs.univ-paris-diderot.fr/services/pepATTRACT/	N/A	Global docking procedure: (i) generation of peptide structures by threading peptide sequence onto three peptide conformations (alpha-helix, polyproline-II or extended); (ii) global rigid-body docking of peptide structures within binding pocket; (iii) scoring with ATTRACT score; followed by (iv) flexible refinement of models with iATTRACT [53]. Both peptide and interacting residues of receptor are fully flexible	Tested on unbound complexes from PeptiDB [45] database: near-native or better models obtained; also available in a local-docking version, pepATTRACT-local [53], which additionally uses user-provided list of residues involved in binding	[42,53]
MDockPeP	Not publicly available	N/A	Global docking procedure: (i) MODELLER [69]-based prediction of peptide conformation using fragments of monomeric protein structures; (ii) global rigid docking using a modified version of AutoDock Vina [33]; (iii) scoring with knowledge-based ITScorePeP method; and (iv) fully flexible local optimization	Tested on complexes from PeptiDB [45] database: medium-resolution or better models obtained	[40]
CABS-dock	http://biocomp.chem.uw.edu.pl/CABSdock and as a standalone version	N/A	Global docking procedure: (i) explicit fully flexible docking simulation; and (ii) clustering-based scoring. Receptor flexibility limited by default to small backbone fluctuations, but can be increased to include selected receptor fragments	Tested on complexes from PeptiDB [45] database: medium-resolution or better models obtained; can be used for global docking with large-scale conformational rearrangements of both peptide and receptor [44,49]	[44]
AnchorDock	Not available publicly	Pc (peptide in extended conformation)	Global docking procedure: (i) simulation of folding of free peptide in implicit solvent; (ii) ANCHORSmap [63]-based prediction of anchoring spots; (iii) simulated annealing MD simulation of peptide in proximity of anchoring spot; and (iv) clustering and energy-based scoring	Tested on custom set of 13 complexes: near-native or better models obtained in most cases	[43]
ClusPro PeptiDock	https://peptidock.cluspro.org/	N/A	Global docking procedure: (i) motif-based prediction of peptide conformation; (ii) PIPER [48] rigid-body docking; (iii) scoring according to structural clustering; and (iv) minimization of final structures	Tested on set of 16 complexes from PeptiDB [45] and additionally on set of five newly published structures: medium-resolution models obtained for all but three cases [41]	[41]
PIPER-FlexPepDock	http://piperfpd.furmanlab.cs.huji.ac.il	N/A	Global docking procedure: (i) prediction of peptide conformation using Rosetta fragment picker; (ii) PIPER [48]-based rigid-body docking; (iii) refinement using Rosetta FlexPepDock [27] and (iv) clustering and scoring according to Rosetta energy function	Tested on set of 27 complexes from PeptiDB [45]: near-native conformation obtained in 70% of bound cases and 41% of unbound cases	[39]

[a] All programs require as input a receptor structure and a peptide sequence. Additional requirements are as follows: PcB, initial peptide conformation in the binding site; Pc, initial peptide conformation; B, information on binding site of receptor.
[b] Model quality: peptide backbone-RMSD to experimental structure: subangstrom: <1 Å; near-native: <2 Å; medium: >2 Å and <5 Å (upper limit can vary slightly depending on method).

peptide docking is to treat the protein and the peptide input conformations as rigid and to perform exhaustive rigid-body docking. More sophisticated methods automatically predict peptide conformation using a sequence provided by the user. Their pipelines usually has three stages: (i) generation of input peptide conformations; (ii) rigid-body docking; and (iii) scoring of the models and/or refinement. As presented in Table 1, the peptide conformation can be predicted using various strategies (e.g., using structure fragments from monomeric protein structures [40,41], threading the sequence onto a predefined set of template conformations [42], or simulating peptide folding in solution [43]). Generation of peptide conformations can also be combined with global docking in one explicit simulation. This is possible in the CABS-dock method [44], which starts from random peptide conformations and induces their conformational changes only by interactions with a flexible receptor. Alternatively, global docking can be combined with predictions of the binding site. This approach is used in AnchorDock [43], which automatically identifies potential binding sites and docks a flexible peptide in the proximity of these spots. High-accuracy predictions were recently obtained by PIPER-FlexPepDock [39], a global-docking tool that uses fragments extracted from solved monomer structures based on sequence and (predicted) secondary structure similarity to mimic the peptide conformational ensemble with significant representation of bound-like peptide conformations. The ensemble is then rigid body-docked using exhaustive Fast Fourier Transform-based docking with PIPER followed by flexible all-atom refinement to near-atom resolution by Rosetta FlexPepDock (Fig. 2).

Challenges

We identify at least three major challenges to protein–peptide docking: (i) modeling significant conformational changes of both peptide and protein molecules (flexibility problem); (ii) selection of the highest accuracy structure out of many generated models (scoring problem); and (iii) integration of experimental data and computational predictions into the protein–peptide docking scheme (integrative modeling).

Flexibility

Docking difficulty and the prediction accuracy depends on the number of flexible bonds of a peptide and, therefore, not only on peptide size, but also on its defined secondary structure. Small-molecule docking programs are usually limited to very short peptides, up to a few residues [33,36]. Most of the docking methods presented in Table 1 were tested on the PeptiDB set which comprises peptides that are 7–15 amino acids long. Within this size range, acceptable results are usually obtained for well-structured, helical or beta-sheet peptides. Modeling unstructured peptides is more difficult and feasible for peptides up to ten residues. Modeling longer peptides can be overcome by docking peptide fragments followed by their merging [37,38].

Receptor flexibility upon binding can range from small side-chain reorganization to large-scale backbone rearrangements [46,47]. The difficulty of docking increases with increasing receptor conformational changes, and explicitly addressing backbone flexibility can become a major challenge [20,46]. The most straightforward approach is to perform rigid-body docking,

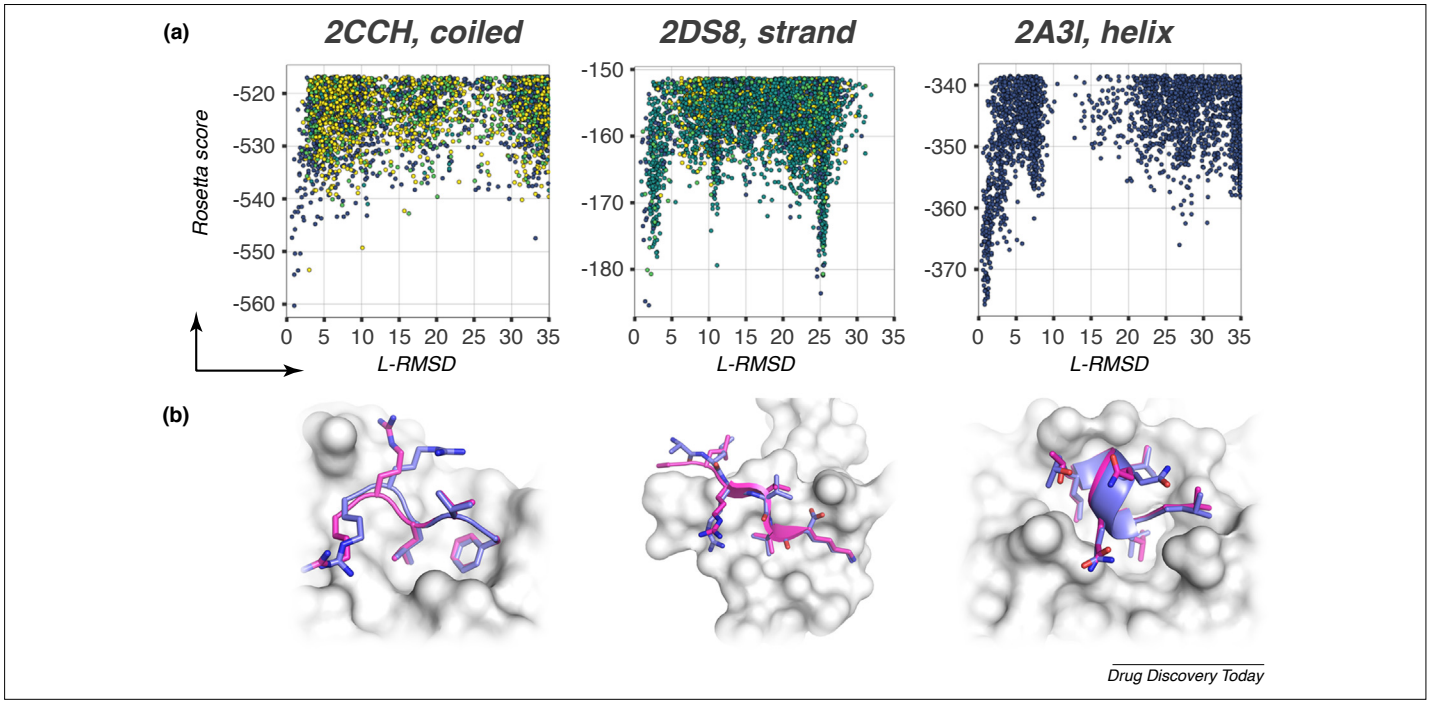

FIGURE 2

Examples of global docking results obtained with PIPER-FlexPepDock [39]. The picture shows: (a) energy landscapes (obtained from docking the peptide to the free receptor, including receptor flexibility; dots are colored according to the similarity of the docked fragment to the bound peptide conformation, from the highest in blue to green to the lowest in yellow); and (b) comparison of predicted models to experimental structures (models are presented in blue, experimental peptide structures [2CCH, 2DS8 and 2A3I complexes] in magenta). The PIPER-FlexPepDock method combines: (i) generation of peptide conformations based on fragments from protein monomer structures; (ii) rigid-body docking; and (iii) high-resolution refinement of a few hundred of the top-scored models (for details, see Table 1 in the main text).

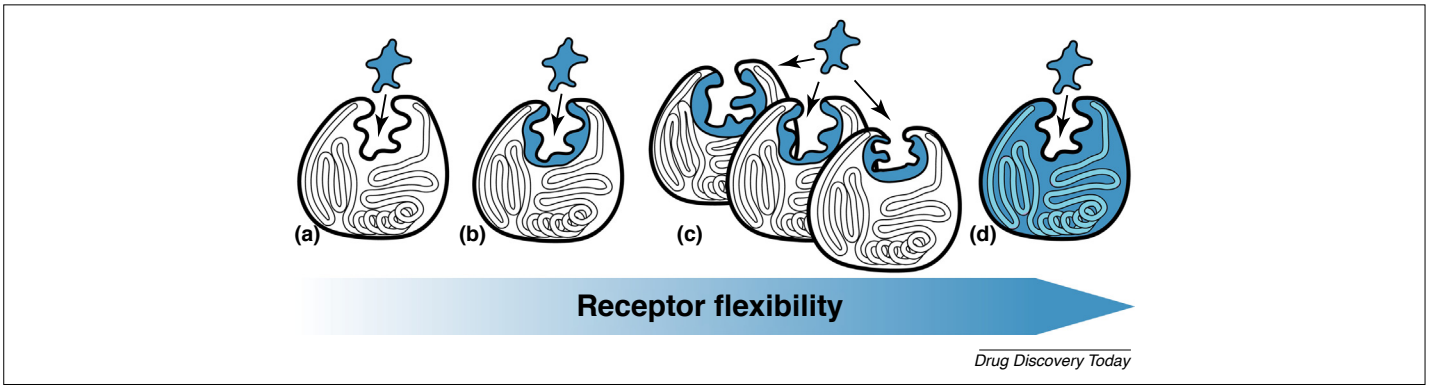

FIGURE 3

Approaches to modeling flexibility of a protein receptor in protein–peptide docking. The flexible elements of the system are marked in blue: (a) rigid-body docking; (b) docking with flexible side-chains in the expected binding site; (c) ensemble docking of different protein conformations; and (d) docking with a flexible protein backbone allowing for large-scale rearrangements.

ignoring receptor flexibility (Fig. 3a). The main advantage of this method is the low computational cost, which enables exhaustive sampling of the receptor surface in search for a binding site. Rigid-body docking is often used as the main or one of the main components of global docking protocols (Table 1). However, those protocols allow at least for side chain flexibility in other modeling steps (Fig. 3b, Table 1). Other protocols use implicit flexibility models: for example, Gold [34] uses ensemble docking (Fig. 3c), whereas protocols such as DynaDock [28] and PIPER [48] use soft potentials to mimic receptor flexibility. Finally, coarse-grained protein models can be used to model large-scale backbone rearrangements, for example of disordered regions of significant length [49] or a loop region close to the binding site [50] (Fig. 3d).

Scoring

The successful identification of the most accurate model among the large pool of docking results remains a challenge [20]. In most cases, the top-ranked models are of lower quality than the most accurate models present in the docking results. Most docking tools use energy-based scoring methods for model ranking. For example, Rosetta FlexPepDock [27] uses the Rosetta energy function or its modification in the *ab initio* variant [30]; HADDOCK [32] uses a method based on binding free energy calculated with the dampened Molecular Mechanics Poisson–Boltzmann Surface Area (MM-PBSA) algorithm [51]; pyDockWEB [52] uses a semi-empirical physicochemical scoring function; pepATTRACT [53] picks the best models according to the complex binding energy derived from short MD simulations [54]; CABS-dock uses knowledge-based scoring functions [44]; and BiPPred method MM-PBSA affinity calculations [57]. Except for energy-based scoring, some protein–peptide docking tools use additional methods to improve model selection, such as structural clustering and selection of the largest clusters [44,49,55], incorporation of coevolutionary information [56] or mutagenesis data [20], comparison with template structures [15], or sequence-based predictions [57]. CAPRI competition results show that hybrid methods, based on mixed scoring functions, generate the best protein–peptide docking results [20]. For example, including coevolutionary information in the scoring procedure yielded outstanding results in a recent CAPRI competition [56].

Integrative modeling

Using available experimental data can significantly increase docking accuracy: for example, nuclear magnetic resonance (NMR) experiments can be used to identify native contacts, whereas small-angle X-ray scattering (SAXS) or high-resolution cryo-electron microscopy (cryo-EM) provides the shape of the bound complex [58]. However, making use of experimental data can be challenging because of data ambiguity. As an example, the HADDOCK server [31] enables the user to translate experimental data into ambiguous interaction restraints that can be used in docking [32,59,60]. Docking methods can also be helpful in the interpretation of ambiguous data that describe a binding mechanism [49,61]. Beyond the use of experimental data, prediction accuracy can also be improved by integrating docking tools with other computational techniques, such as molecular dynamics-based approaches [62], key interactions [63], and prediction of the binding site [1]. In case of prediction of the binding site, it is advisable to use methods dedicated for detecting peptide binding sites [64–66] (a recent book [1] provides an in-depth guide to such computational tools). Traditional methods for small molecule-binding site prediction might not be well suited to differentiate the binding sites of nonpeptide ligands and protein–protein interactions from protein–peptide binding sites [67]. Finally, different predictions obtained with various protein–peptide docking tools can be used in a meta-analysis approach to detect the protein–peptide interface hotspots [22].

Concluding remarks

Recent interest in peptide therapeutics has triggered rapid development of the field of protein–peptide docking [1,2,4,5]. So far, several successful protein–peptide docking applications in drug design have been reported, including virtual inhibitor screening [17,18], prediction of subangstrom-quality models [6,11,12,14,15], interpretation of experimental data [13,49], specificity prediction [1,15], and design of interfering peptides targeting protein–protein interactions [5,6,26].

Answers to practical questions, such as: ‘‘how accurate can docking be?” or ‘‘how many poses should one consider to have a chance to get a correct pose?”, are not straightforward. They depend on the case, the method used, and, in addition, the success

measures are not easy to establish. For example, the accuracy measured as the commonly used RMSD to the experimental structure is not always the best criterion of docking success. It was recently shown that low-resolution (low-RMSD) models could provide high-quality information on the complex structure, correctly identifying most of its key interactions [22]. Presently, structure-based drug discovery and design uses protein–peptide docking methods most commonly as tools supporting experimental work, for example for the interpretation of ambiguous experimental data, identification of key interactions, or simply for complex visualization. We expect that protein–peptide docking applications will expand as advances in flexibility modeling, scoring methods and integrative modeling are made.

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