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Peptiderive server: derive peptide inhibitors from protein–protein interactions

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ABSTRACT

The Rosetta Peptiderive protocol identifies, in a given structure of a protein–protein interaction, the linear polypeptide segment suggested to contribute most to binding energy. Interactions that feature a 'hot segment', a linear peptide with significant binding energy compared to that of the complex, may be amenable for inhibition and the peptide sequence and structure derived from the interaction provide a starting point for rational drug design. Here we present a web server for Peptiderive, which is incorporated within the ROSIE web interface for Rosetta protocols. A new feature of the protocol also evaluates whether derived peptides are good candidates for cyclization. Fast computation times and clear visualization allow users to quickly assess the interaction of interest. The Peptiderive server is available for free use at http://rosie.rosettacommons.org/peptiderive.

INTRODUCTION

The ability to manipulate precisely a specific protein interaction is of primordial importance for the study of its functional role, as well as for targeted drug design (1). Traditionally, drug design focused on targeting enzyme substrate binding pockets, whereas protein-protein interactions (PPIs) with their often flat interfaces have been considered more difficult to target. However, remarkable advances have been reported for the challenge of inhibiting PPIs (reviewed in (2–4)). Crucial for this success has been the discovery that within these flat surfaces a restricted number of 'hot spot' residues play a crucial role in binding: when mutated to alanine, the binding affinity is significantly reduced (5). Importantly, protein interactions are often mediated by a single linear peptide stretch, or 'hot segment' that can cover several hot spot residues (6). Knowledge of the location and binding mode of such hot segments can provide an optimal lead for rational drug design (7). Thus, while features such as hot spots have long been studied, expansion to the supporting hot *segment* provides a new viewpoint on these interactions.

The Rosetta Peptiderive protocol developed by our group identifies, given the structure of a protein complex, the hot segments in a PPI, namely, the linear peptide segment estimated to contribute most significantly to binding between the protein partners (6). Based on approximation of the binding energy of the derived peptide segment to the protein partner (and compared to the binding energy of the full protein interaction) we, and others, reported that a significant fraction of protein interactions are mediated predominantly by such a linear hot segment (6,8). Such peptides often exhibit calculated binding energies similar to those of known peptide–protein interactions, and tend to retain their binding conformation also out-of-context of the full protein, as demonstrated by FlexPepDock refinement (9) of the derived peptide–receptor complex (6).

These features suggest that *hot segments* could compete with the proteins they were originally derived from for binding to the partner. Indeed, we recently were able to derive an agonist of the MD2–TLR4 interaction, starting from a hot segment identified by the Peptiderive protocol (10). Similarly, a peptide cut out from the Ubiquitin E3 Ligase SCF^{Fbx4} inhibited binding to TRF1 (IC50 = 206 μM (11); this peptide was estimated by Peptiderive to provide 47% of the complex binding energy). As yet another example, for the proteasomal gankyrin—ATPase complex, a dominant peptide EEVD derived from the latter was able to inhibit this interaction (IC50 = 50 μM (12); this peptide is included in a dominant decamer segment suggested by Peptiderive to contribute 49% of the complex binding energy). Inhibitory peptides are usually further stabilized by introducing constraining features to lower the entropy cost for binding, for example by secondary structure mimetics (13–15) or by cyclization (16), e.g. by introducing a disulfide bridge via mutation to cysteine of the peptide terminal residues (10). Stabilisation of peptides by disulfide bonds has also been suggested for application to loops at interfaces (17,18). Practical relevance of these derived peptides may also be inferred by comparing them to existing drugs that inhibit specific

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PPIs. Such drugs are often developed using experimental chemical screens without the use of structural information. Notably, in all cases where the (subsequently solved) structure of the drug bound to the protein is available (19), we observed an overlap of the derived hot segment with the PPI inhibitor (7). Altogether, these accumulating evidence highlight the relevance of the hot segments detected by Peptiderive as means of detecting 'druggable' interfaces, toward applications in drug design.

The Peptiderive protocol is part of the Rosetta macromolecular modeling framework (20). In order to make it widely accessible to the community, we have developed a web server for Peptiderive within the framework of the ROSIE (**R**osetta **O**nline **S**erver that **I**ncludes **E**veryone) web interface for Rosetta protocols (21). Compared to the previously published version (6), the protocol implemented for the server uses the most recent state-of the art Rosetta scoring function (currently Talaris2014 (22)) and provides information about derived peptides that can be closed by a disulfide bridge (see below). It also includes an interface with RosettaScripts (23), a coherent report format and several bug fixes. The results obtained with this new version are similar to those obtained in the previous study (see Supplementary Figure S1).

Related servers

The Peptiderive server joins a varied range of servers that provide access to tools for interface analysis and handles for targeted drug design, starting from a solved protein complex structure (e.g. alanine scanning, by computation of energy changes (24,25) or by using machine learning approaches based on structure and sequence ((26–28); reviewed in (29)). Beyond individual hotspot residues, local *clusters* of hotspots are identified by e.g. PocketQuery to identify the best target sites on a protein interface (30), similar to the hot segments identified by Peptiderive. Binding sites can also be identified from the structure of the isolated receptor only (e.g. using solvent mapping (31,32)).

ALGORITHM

The basic Peptiderive protocol (Figure 1)

Peptiderive accepts as input a structure of a protein pair complex, with one of the proteins defined (by the user) as the receptor and the other as the partner (Figure 1A). The structure is first minimized in order to remove local clashes without changing the structure significantly. Then, a sliding window (of length defined by the user) goes over the partner chain: at each position of the protein, a peptide fragment of the given window size is isolated (Figure 1B), charges are added to the termini, the resulting peptide–protein complex is modeled and the estimated peptide binding energy is calculated (using the Rosetta energy function; see (6) and Supplementary Data for more details) (Figure 1C). After going over all overlapping peptides, the peptide contributing most significantly to binding is selected and reported (Figure 1E). Conceptually, this protocol is similar to experimental peptide arrays, in which an array is prepared that contains overlapping peptides derived from one protein, to which the protein partner is added to identify the region(s) of interaction (33).

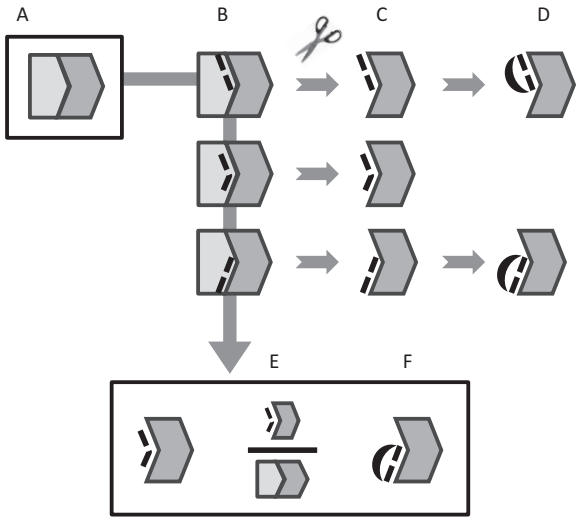


Figure 1. Scheme of the Peptiderive protocol. Given a structure of a protein–protein complex (a receptor and its partner, in dark and light grey, respectively) (**A**), a sliding window of user-defined size is run along the partner protein (**B**), a peptide is cut out, and its binding energy to the receptor is calculated as described in (6) and Supplementary Data (**C**). Peptides with the appropriate geometry are cyclized by a disulfide-bond by mutating their leading and trailing residues to cysteine (**D**). The output highlights the peptides with the largest contribution to binding energy (relative and absolute) (**E**), as well as information on cyclic peptides (**F**) (see Figure 2).

Stabilization by closure of peptides via a disulfide bridge

We assess whether peptides may be further stabilized by cyclization via a disulfide bond (Figure 1D and F). If the flanking residues of a hot segment are close enough in space (between 3–5Å Cβ–Cβ distance and 4.5–6.5Å Cα–Cα distance for glycine), we mutate these residues to cysteine and connect them by a disulfide bond (resulting in a peptide that is two amino acids longer than the requested length). The cysteine side chains are repacked to allow formation of the disulfide bond, followed by minimization of the cyclic peptide within the context of the protein, and the binding energy is evaluated again. To conserve computation time, we only consider peptides for cyclization if they contribute significantly to binding (defined here as $\geq$35% of the total binding energy, a value that can be changed in the standalone version).

Generalized protocol

For a given protein complex of N chains, the algorithm will iterate over all (N choose 2) protein pairs in the complex, and each such pair will be passed to the algorithm twice—once with one protein as the receptor and the other as the partner, and a second time the other way around. Optionally, the calculation may be restricted to consider certain chains only as receptors, or only as partners for the interaction.

Output of algorithm

A report is prepared for each receptor–partner pair and peptide length specified (see Figure 2 and below), with a list of the absolute and relative binding energy of peptides cut out from each sliding window position. Peptides that contribute most to the interaction energy ('best linear peptides') are highlighted at the top of the report. Additionally, if any cyclic peptide models were produced, they are listed separately ('best cyclic peptide'). We note that the binding energy calculated for the cyclic peptide is not directly comparable to that of a linear peptide, both because of the different length and since the context has changed due to mutations. Therefore, we highlight cyclic peptides with favorable energy either in their mutated cyclic state or in their native state.

WEB SERVER INTERFACE

Inputs

The infrastructure of the ROSIE web service (21) was used to create a web-server frontend for the Peptiderive protocol. The user provides the input structure by either uploading a Protein Data Bank (PDB) (34) structure format file of coordinates, or by specifying a PDB ID. Optionally, the user may specify the size of the peptide window and a list of chains to be restricted to a certain role (receptor or partner). As with other job submissions to the ROSIE web service, the user can choose whether to make the computational job inputs and outputs publically available, and whether to provide an e-mail and opt to get notifications of the job status. Upon submission, the task is queued for computation by a remote computing cluster (see 'Web server methods' section).

Results page

Figure 2 shows an example output for the interaction between the activation domain of the enhancer protein E2 and the helicase domain of the E1 viral initiator protein of human papillomavirus 18 (HPV-18) (PDB ID: 1TUE) (35), for which hot segments identified by Peptiderive provide an appealing lead for designing binders. An image of the receptor-partner complex highlights the location of the 'hot segment' (the peptide that contributes most to binding energy) derived from E2 (Figure 2B). In this case, a 13-mer peptide contributes 56% of the binding energy. To its right, an image of a receptor–peptide model shows the details of the peptide in stick representation (Figure 2C). If a relevant cyclic peptide can be generated, it is shown in an additional image to the right (Figure 2D). In this case, a cyclic peptide that contributes 41% of the binding energy was identified. Below, energy contributions of each overlapping peptide window are plotted (and the cyclic peptide is emphasized) (Figure 2E). In addition to the above, we also note that for this interaction, peptides derived from the E1 protein partially overlap a known small molecule inhibitor of the E2 protein (PDB ID: 1R6N (36)).

Besides these graphics, a formatted report file is displayed (Figure 2F), as well as the score table, with the Rosetta score broken down to its different energy terms, of the different models generated during the run (Figure 2G). As with other ROSIE servers, different elements in the results page link directly to the original source output files. In addition, a direct view of the file system is available, so that the user may access and download all input, output, command and log files.

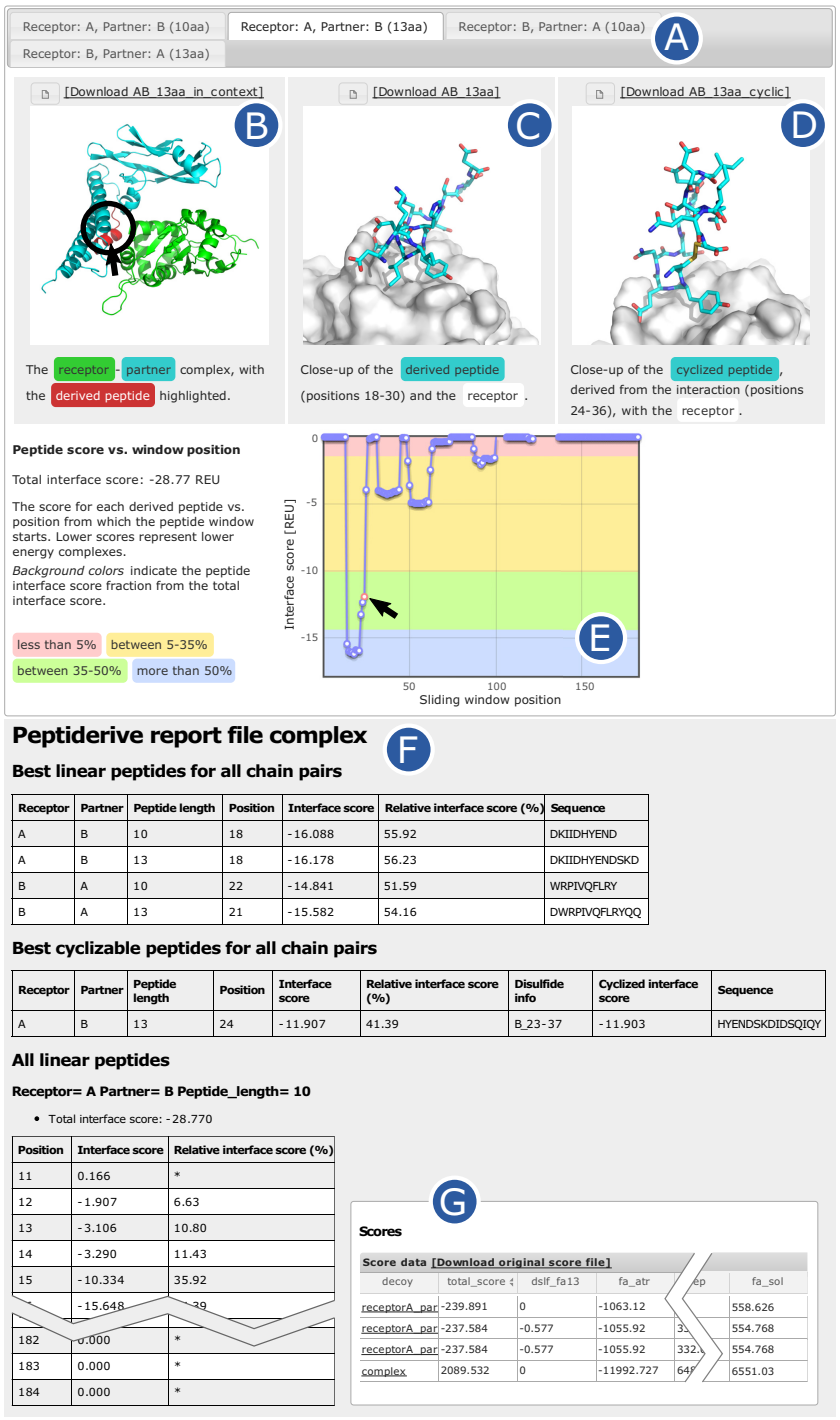
Web server methods

Overview. The ROSIE web service provides the infrastructure for serving web pages, accepting inputs from the user and generating output pages, access control for anonymous and registered users and computational resource management (job queuing). The Peptiderive server is implemented as an 'app' in this service, defining inputs, outputs for the protocol and the formatting of the web pages. After receiving inputs from the user, the app registers the job in the ROSIE queue. Users can monitor the queue; results are made visible in the results page (see above) once the computation completes. The server offers detailed online documentation.

Access control. The server has full, free guest access, similar to other ROSIE services. Jobs can be made private, disallowing anyone but the submitter to view the inputs or outputs, either by access control (for registered users) or using a private URL given upon submission (for anonymous users, or for registered users who wish to share their results with specific people; anyone with the URL may access the job, without the need to supply credentials). A priority bonus is given to jobs that are made public, as well as to jobs from registered users (the bonus is cumulative). For more detail, see (21).

Software infrastructure: protocol. Rosetta version 2016.11 (freely available to academic users) is used in the present server implementation. User inputs from the submission page are inserted into a RosettaScripts XML script template (see Supplementary Data). The RosettaScripts program (23) runs on a single processor. PyMOL (www.pymol.org) is used to generate graphical representations of the protein–protein and protein–peptide complexes. The 'marked' Javascript library (https://github.com/chjj/marked by Christopher Jeffrey) is used to display the report file.

Performance, system architecture, waiting time. Jobs queued by ROSIE are distributed using computing power from different sources (courtesy of the Gray Lab at Johns Hopkins University, RosettaCommons, > 350 dedicated cores; and of the Stampede cluster of the Texas Advanced Computing Center at the University of Texas, 464K cores that are shared among various projects). The average wait time for jobs in the ROSIE job queue is ∼1 day, even though this is affected by priority bonuses given to registered users. Peptiderive tasks typically take minutes to complete after computation commences, depending on the protein size, the number of receptor–partner pairs and the sliding window lengths chosen. An allocation of 0.5G RAM memory is requested for the RosettaScripts program.



Receptor	Partner	Peptide length	Position	Interface score	Relative interface score (%)	Sequence
A	B	10	18	-16.088	55.92	DKIIDHYEND
A	B	13	18	-16.178	56.23	DKIIDHYENDSKD
B	A	10	22	-14.841	51.59	WRPIVQFLRY
B	A	13	21	-15.582	54.16	DWRPIVQFLRYQQ

Receptor	Partner	Peptide length	Position	Interface score	Relative interface score (%)	Disulfide info	Cyclized interface score	Sequence
A	B	13	24	-11.907	41.39	B_23-37	-11.903	HYENDSKDIDSQIQY

Position	Interface score	Relative interface score (%)
11	0.166	*
12	-1.907	6.63
13	-3.106	10.80
14	-3.290	11.43
15	-10.334	35.92
	-15.648	
182	0.000	*
183	0.000	*
184	0.000	*

decoy	total_score	dslf_fa13	fa_atr		fa_sol
receptorA_par	-239.891	0	-1063.12		558.626
receptorA_par	-237.584	-0.577	-1055.92	3	554.768
receptorA_par	-237.584	-0.577	-1055.92	332.	554.768
complex	2089.532	0	-11992.727	64	6551.03

Figure 2. Example results page of the Peptiderive server, showing the identification of hot segments in the HPV-18 E1–E2 protein interaction (PDB ID: 1TUE) (35) (see also text). (**A**) Visualization is provided for each receptor–partner pair and each window length considered. (**B**) Representation of the receptor–partner complex, with the peptide contributing most to the interaction (the 'hot segment') highlighted. (**C**) Representation of the complex of the receptor (surface) bound to the 'hot segment' after it has been cut out from the partner chain (stick representation). (**D**) If relevant, another figure shows the cyclic derived peptide with favorable energy. (**E**) The peptide binding energy for each sliding window position shows how much each overlapping segment of the protein contributes to the total binding energy. Different colored regions indicate different fractions of the receptor–peptide binding energies relative to the total binding energy of the receptor–partner complex (5, 35 and 50% relative energy contribution). If relevant, the energy of the cyclic peptide is highlighted. (**F**) Details of the hot segments (and if relevant, cyclic peptides) are provided in a list, which includes sequence and energy contribution (absolute and relative to the full interaction) of these peptides. (**G**) Finally, the Rosetta score-file of the top peptides allows the inspection of specific energy terms.

CONCLUSIONS AND DISCUSSION

The concept of hot segments is useful for providing starting scaffolds and guidance toward inhibition of important sites at the interface. The many examples where the hot segment derived by Peptiderive overlaps with known PPI inhibitors are a good indicator for its relevance to improved assessment of the inhibition potential of PPIs. The server presented here allows easy access to Peptiderive to the wider scientific community, and it is our hope that by this it will enhance the process of the development of new PPI inhibitors and drugs.

SUPPLEMENTARY DATA

Supplementary Data are available at NAR Online.

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