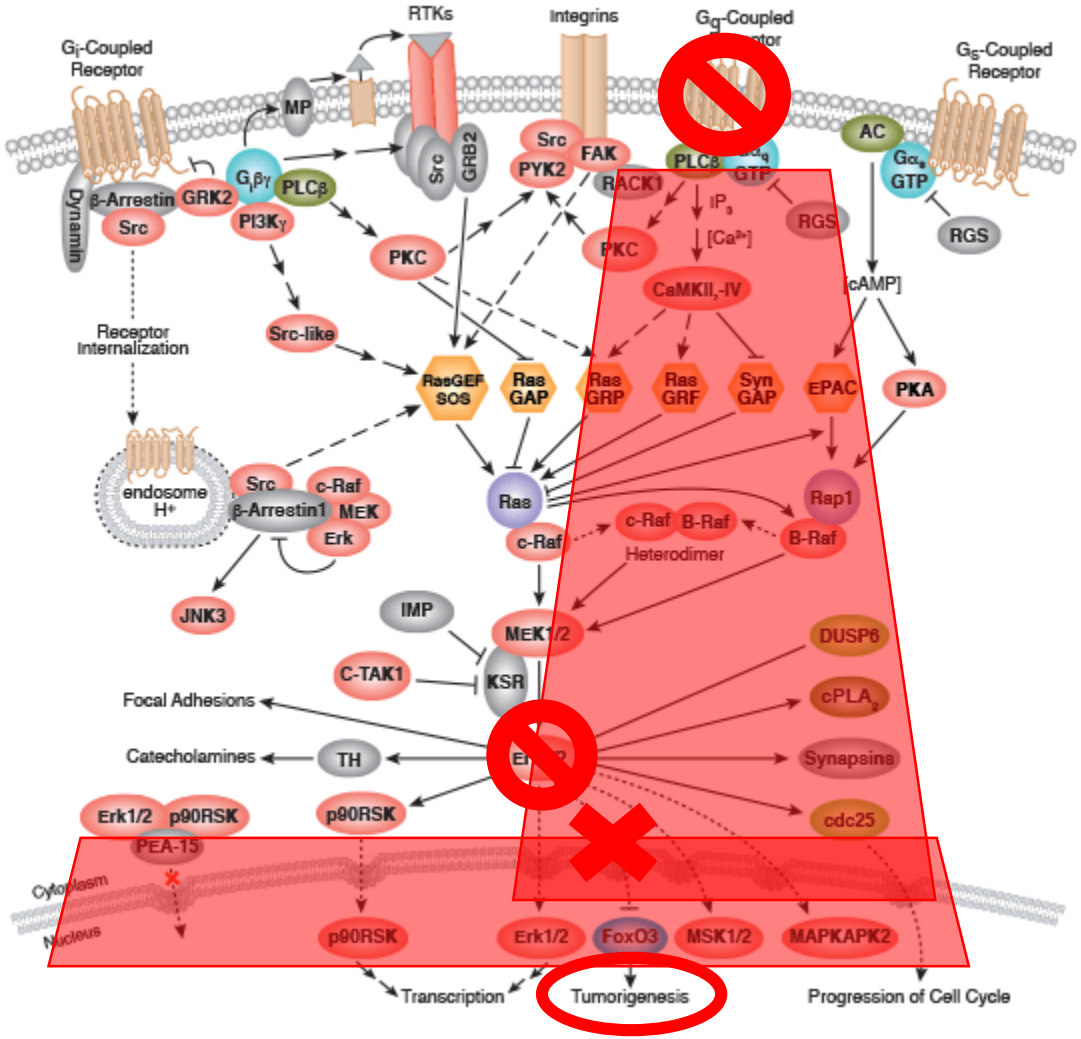
Peptide Design

Rosetta Workshop

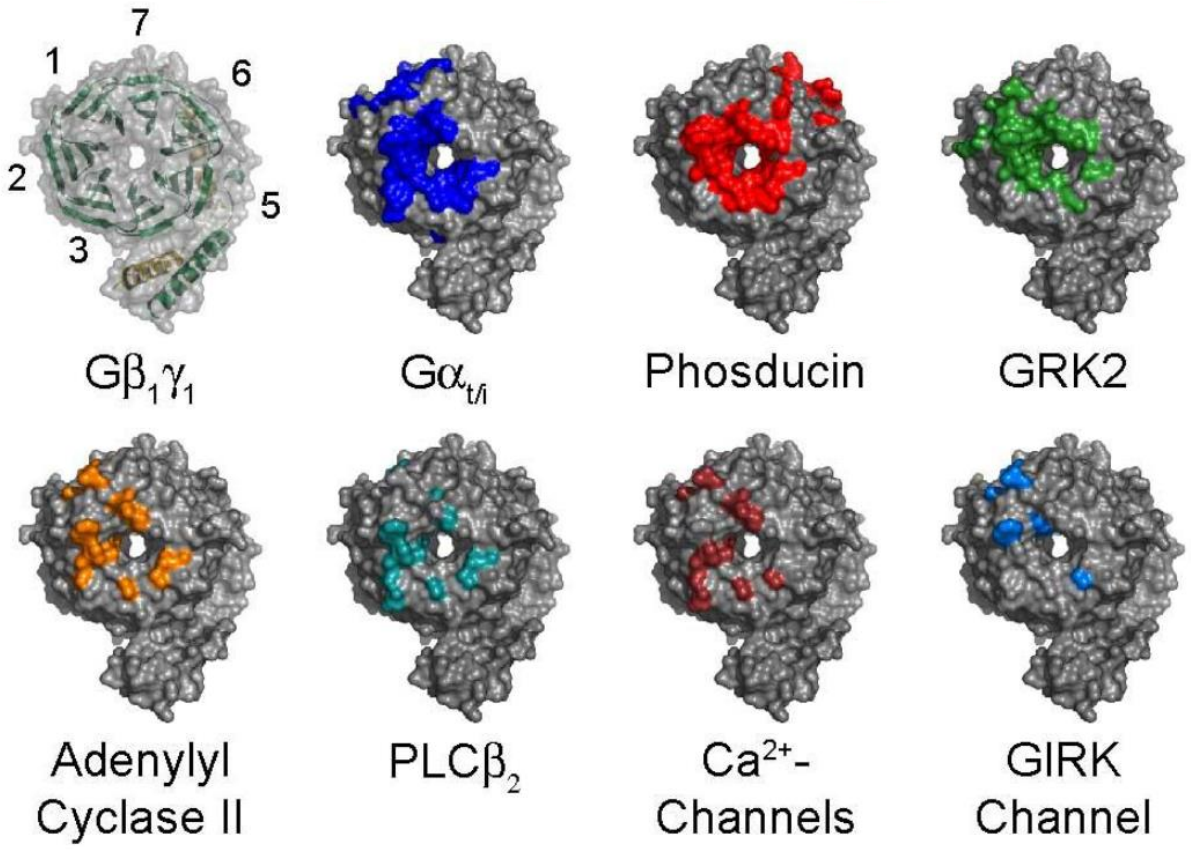
10 May 2018

Protein-Protein Interactions Regulate Majority of Cellular Processes



- Found significantly in signaling and regulatory networks
- Inhibiting a single protein may prove disastrous for the entire network

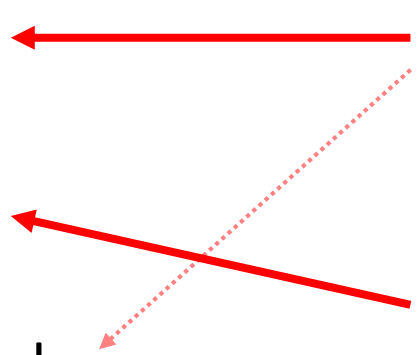
Challenges to Inhibiting Protein-Protein Interactions



- Interactions are often flat surfaces as opposed to pockets
  - Small molecule drugs often need pockets
  - Small molecules are by definition small and may not cover entire binding surface
  - Peptides can bind along surface and with increased specificity than small molecules

Using Peptides to Inhibit Protein-Protein Interactions

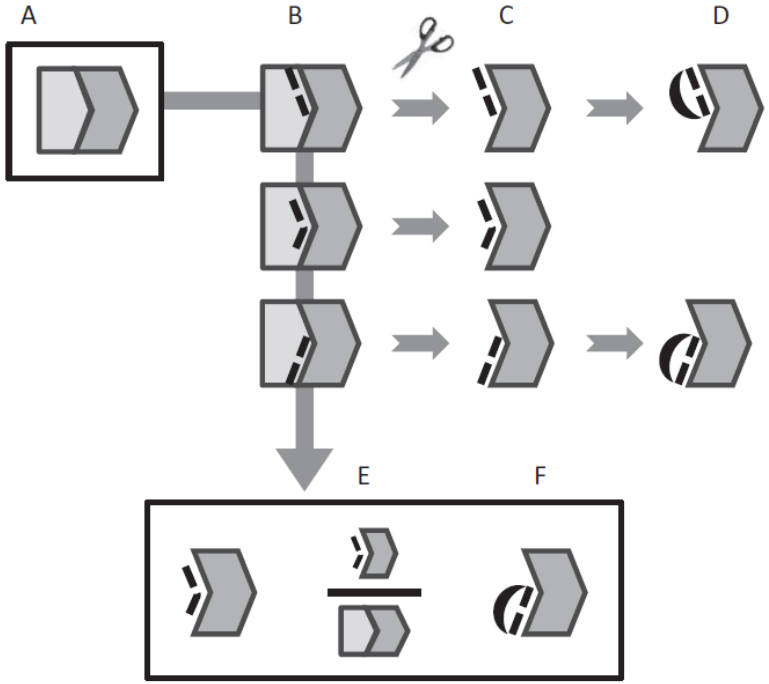
- Derived peptides must bind target with:
  - Comparable affinities
  - Similar binding mode
  - (Would cyclized peptides be suitable?)



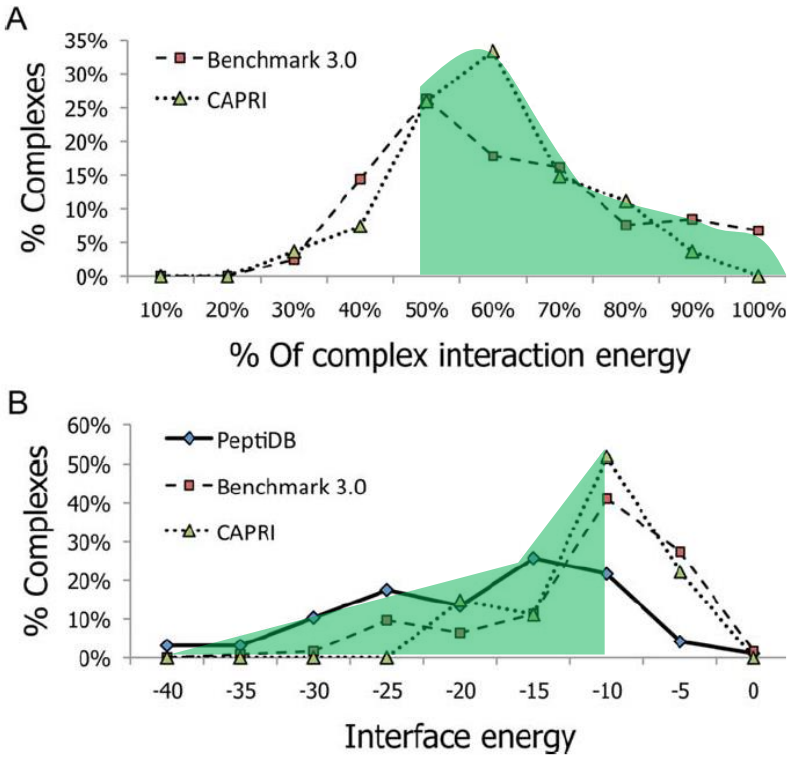
- Protocol for Peptide Design
  - PeptiDerive
    - Peptides derived from protein-protein interaction that contribute majority of binding energy
  - FlexPepDock
    - Are peptides binding in lowest energy state without presence of rest of protein?

PeptiDerive Identifies Peptides from Complex that Make Up the Majority of Binding Energy

PeptiDerive Algorithm



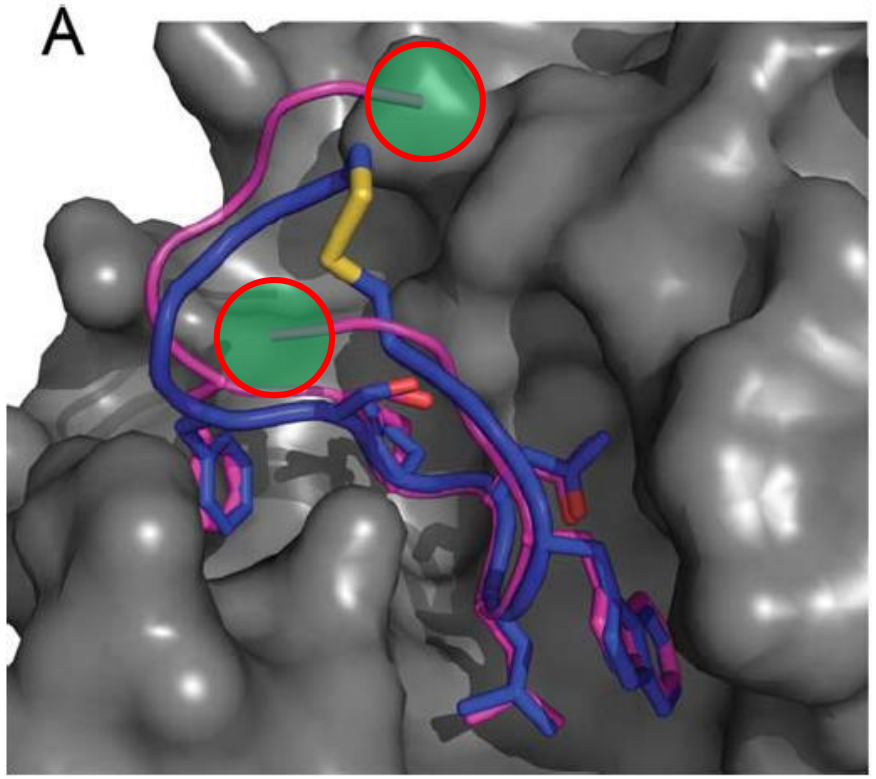
Energetic Analysis



Is Peptide Cyclization Possible?

Cyclization:

- Increases conformational stability
- Reduces biological degradation



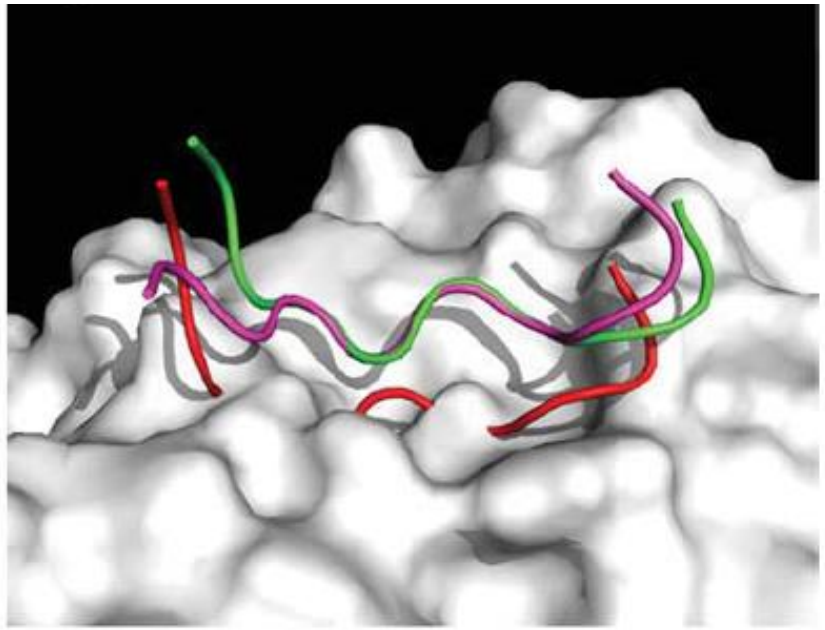
Derived Peptide

Cyclized Peptide

Calculated in PeptiDerive

Does Derived Peptide Bind in Same Orientation?

- Redocking of Peptide (in absence of original protein) allows for energetic sampling of binding surface to ensure correct binding manner

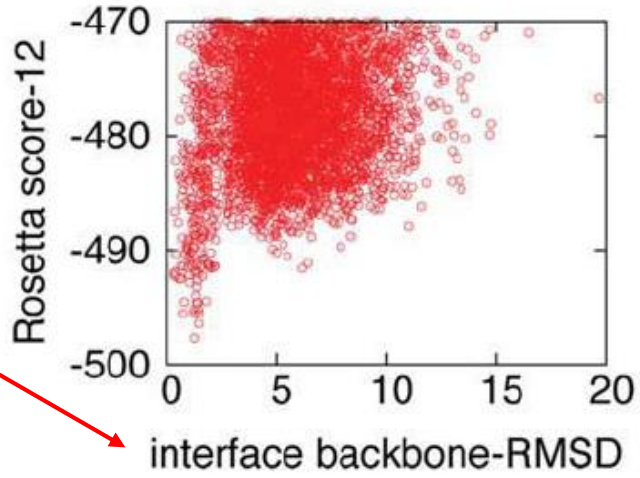


Native

Derived

Redocked

RMSD of peptide interface residues to peptide in its native protein context



Peptide Design Tutorial

1. Submit Protein-Protein Complex to PeptiDerive Server on Rosie
   - http://rosie.rosettacommons.org/peptiderive
   - Necessary input: PDB of protein-protein complex
   - Output: Protein-peptide complex

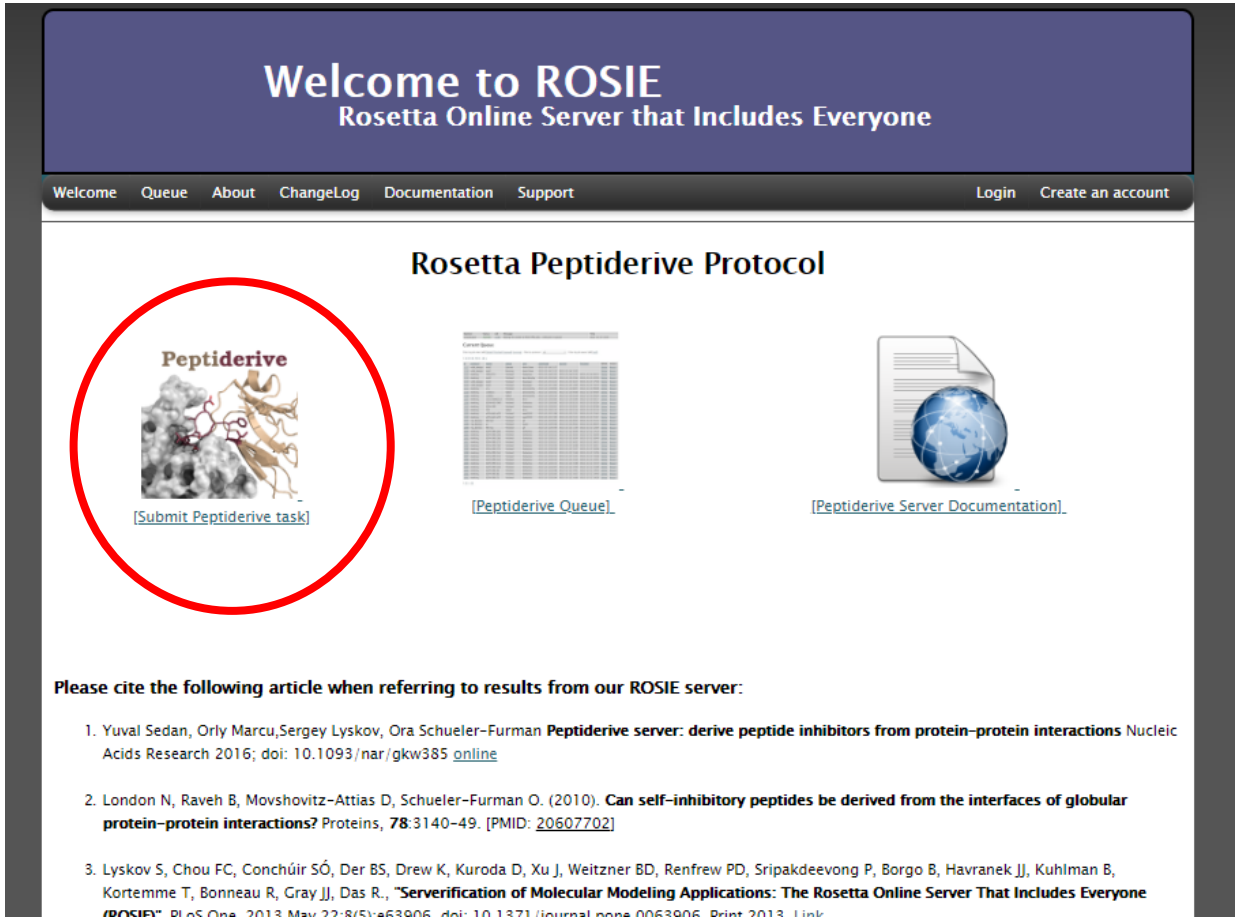
Identifiy peptides that can compete

2. Redock Output Peptide-Protein Complex with FlexPepDock
   - http://flexpepdock.furmanlab.cs.huji.ac.il/
   - Necessary input: PDB of protein-peptide complex (output from PeptiDerive)

Check if the peptide will bind in the same manner without larger protein

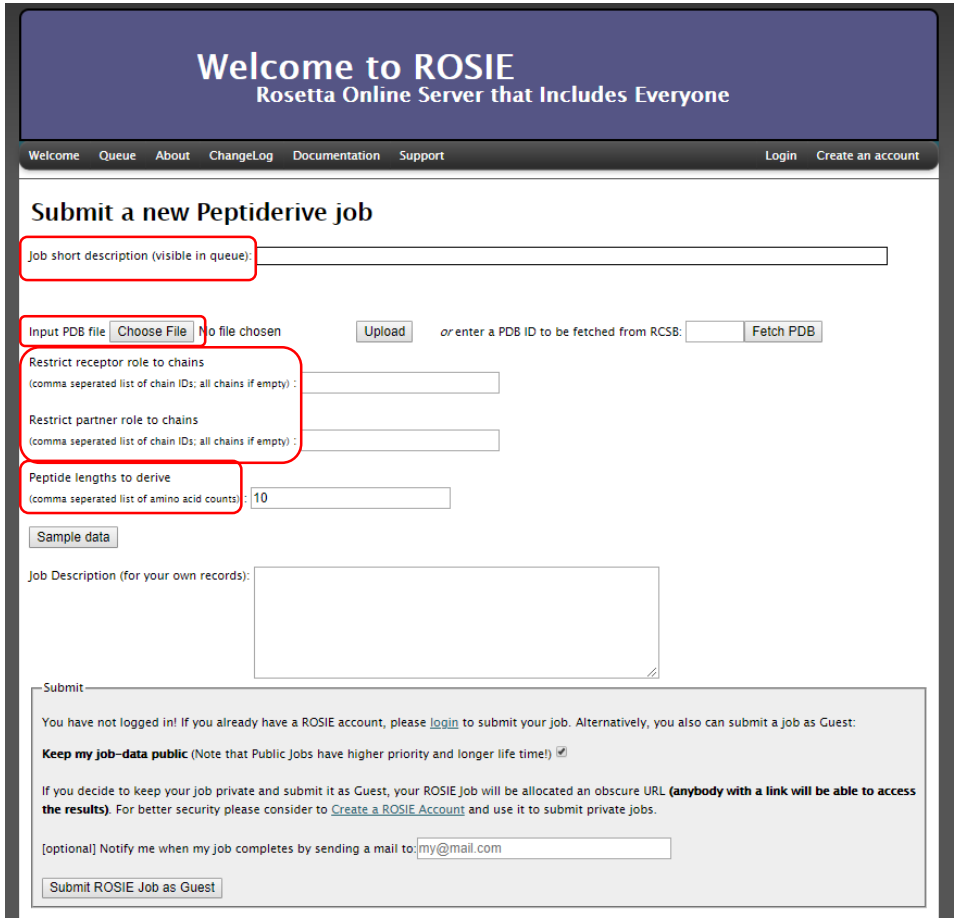
PeptiDerive Server

http://rosie.rosettacommons.org/peptiderive



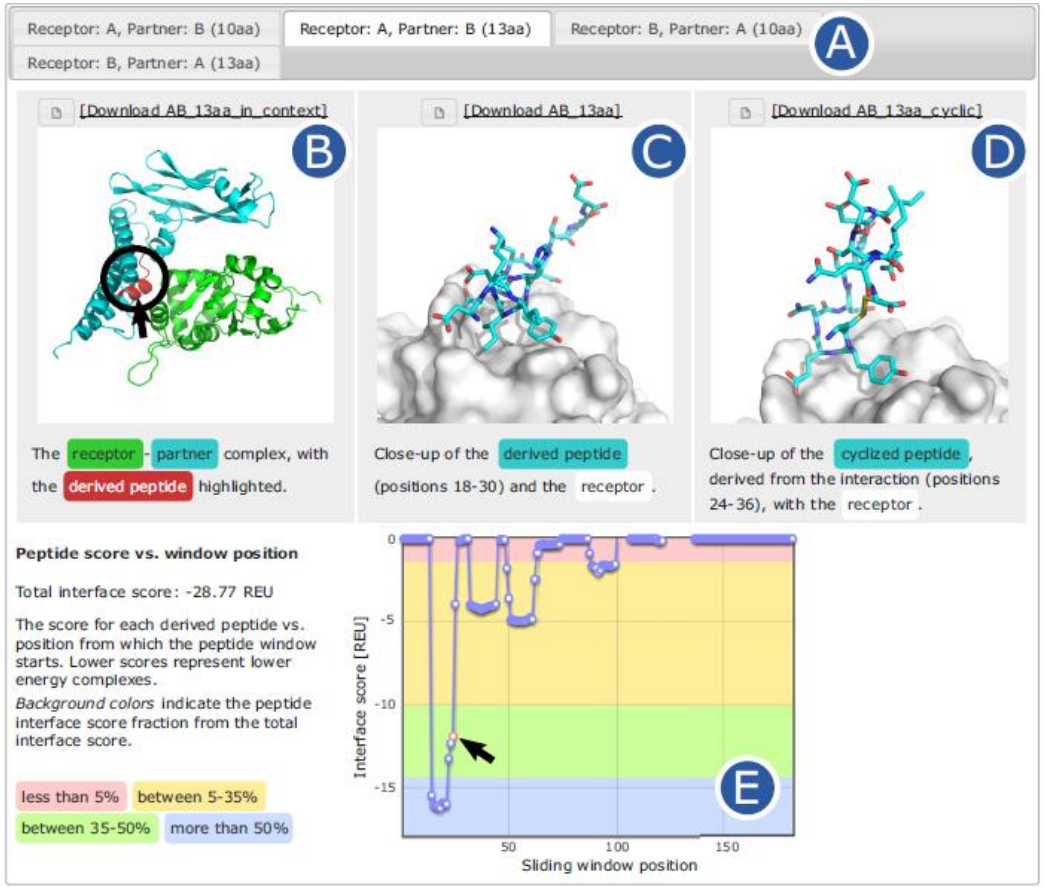
Submitting A Job

1. Public Description
2. **Input PDB (NECESSARY)**
   - Either supply own file or fetch from PDB
3. Specify receptor and partner
   - If not specified, output will contain peptides derivatives of both partners
4. Specify peptide lengths
   - Default is 10



Output from PeptiDerive Server

A. Output Files
B. Visualization of **Derived Peptide** in Context of Complex
C. Visualization of **Derived Peptide**
D. (Visualization of Cyclized Peptide)
E. Energy of Peptide Binding Versus Sliding Window

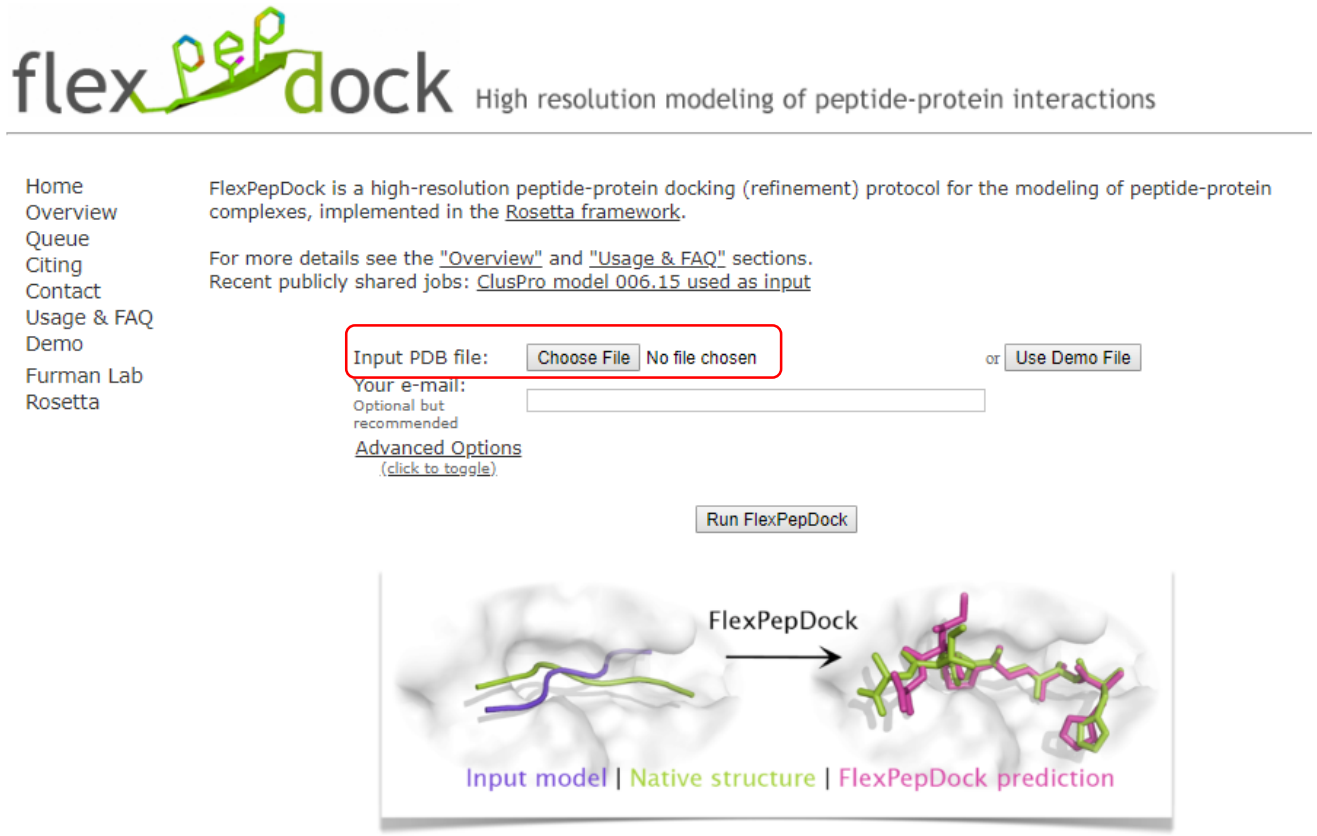


FlexPepDock Server

http://flexpepdock.furmanlab.cs.huji.ac.il/

NECESSARY INPUT:
PDB of Protein-Peptide Complex

Generates 200 models



Receptor B/Peptide A

FlexPepDock Server Output

For download:

- Top 10 model pdbs and scores

flexpepdock High resolution modeling of peptide-protein interactions

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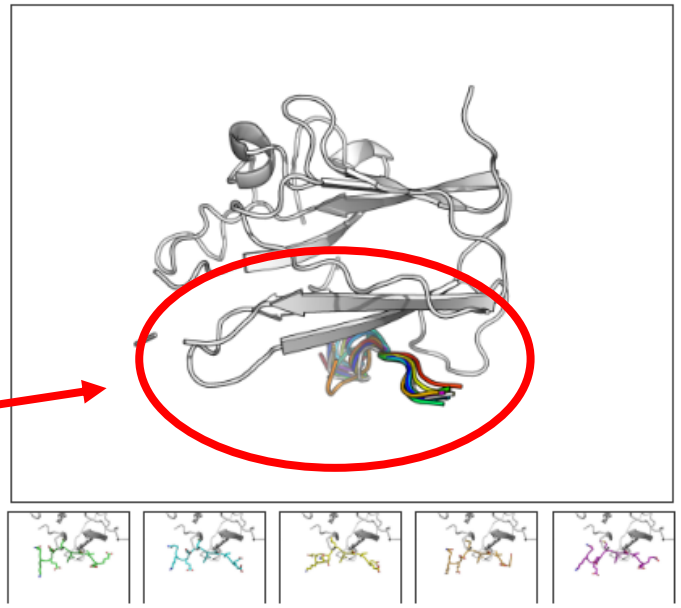
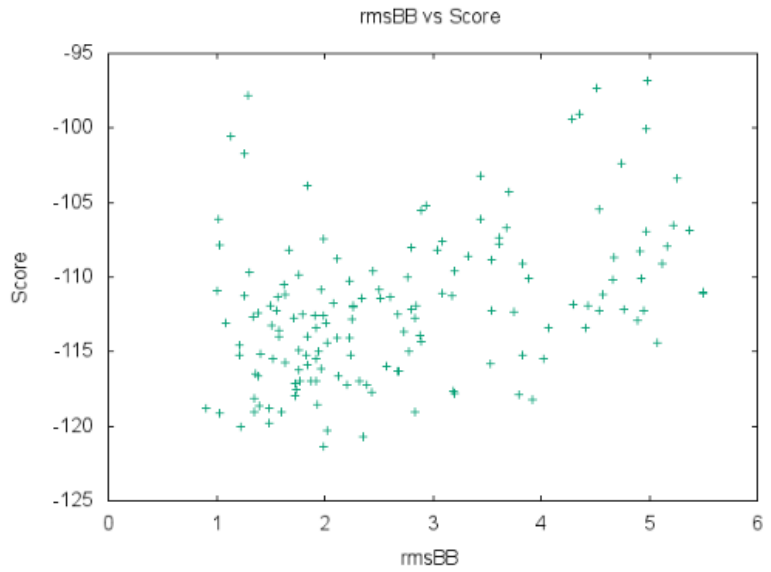
Results for job #9326 (receptorB_partnerA_10aa_best_linear_linear_peptide_complex.pdb):



Check for large movement of peptides here

Score vs RMSD of all 200 poses

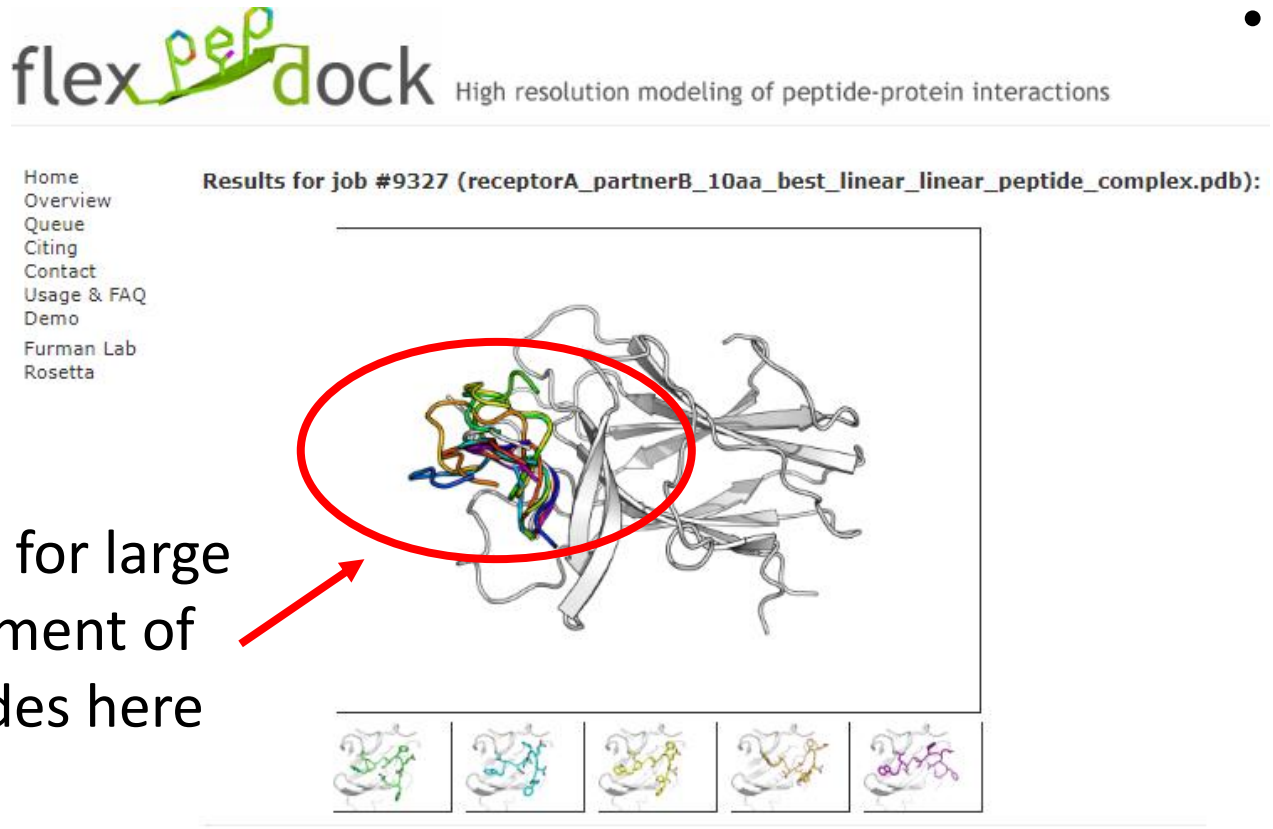


Receptor A/Peptide B

FlexPepDock Server Output

For download:

- Top 10 model pdbs and scores



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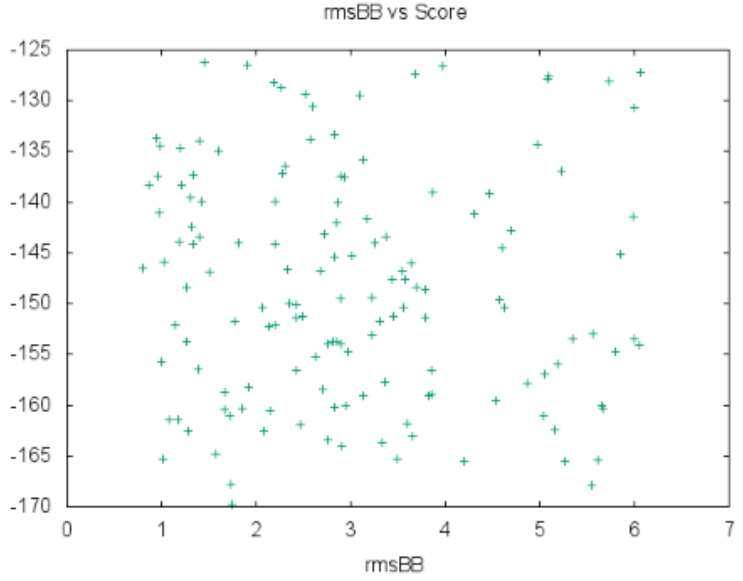
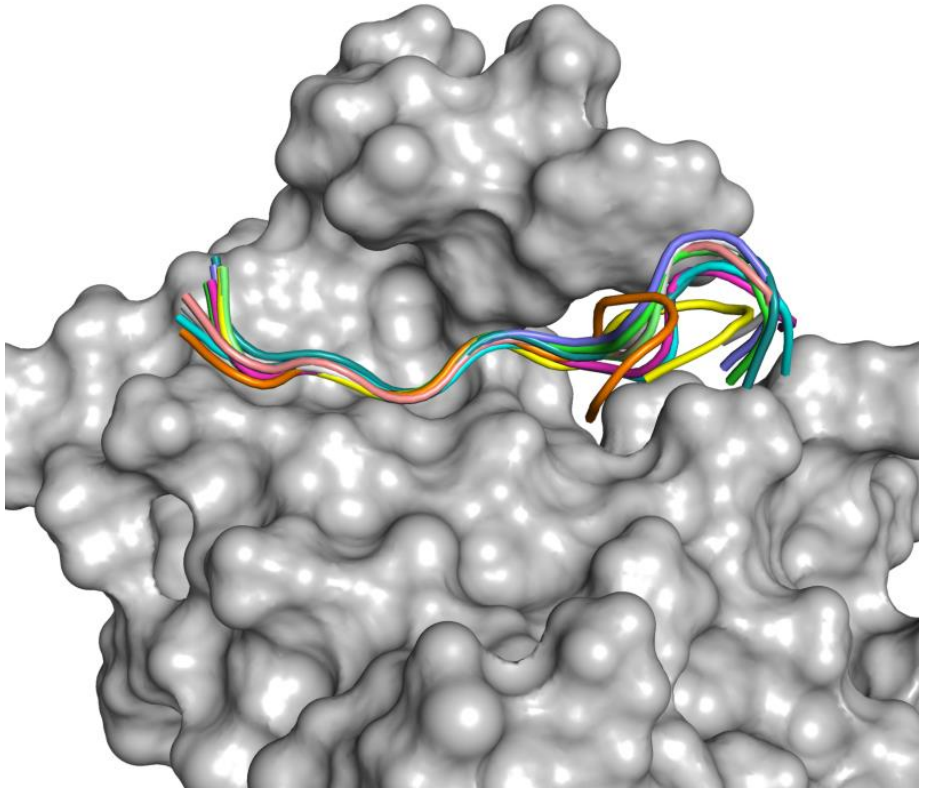
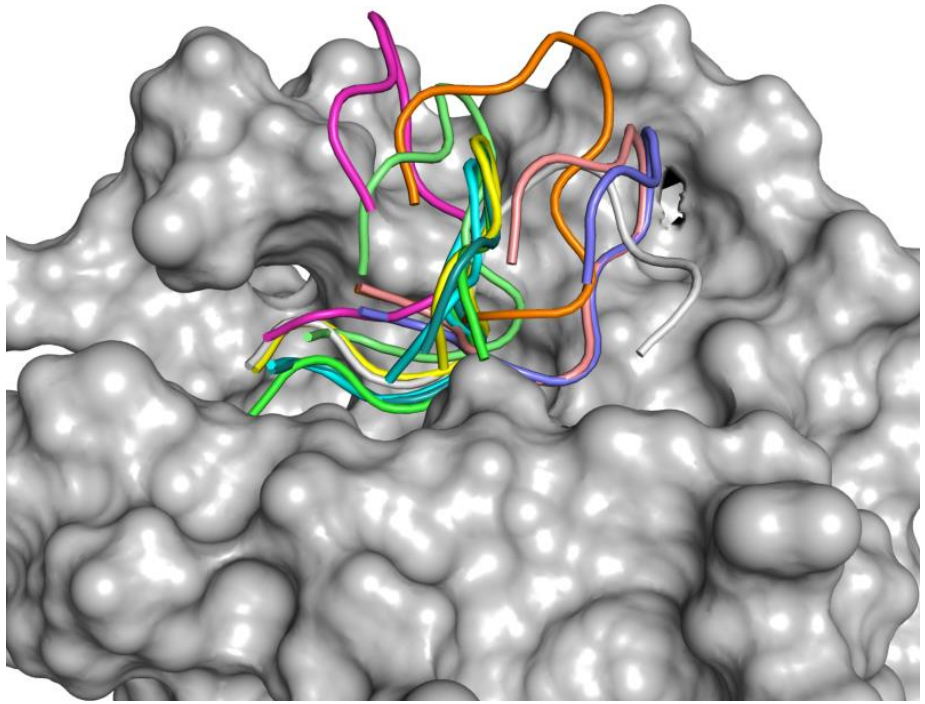


Compare Receptor Pairs

Receptor B



Receptor A



PeptiDerive Without Server

- Utilizes an XML with Rosetta_Scripts
- Needs an input file and an options file

```
{path_to_Rosetta}/main/source/bin/rosetta_scripts.linuxgccrelease \
      -database {path_to_Rosetta}/main/database/ \
      @ options.txt \
      -in:file:s complex.pdb
```

FlexPepDock without Server

- Step 1: pre-pack your initial complex

```
{path_to_Rosetta}/main/source/bin/FlexPepDocking.linuxgccrelease \
      -database {path_to_Rosetta}/main/database \
      -in:file:s start.pdb \
      -flexpep_prepack  -ex1 -ex2aro
```

- Step 2: Refine the pose (100-10000 decoys)

```
{path_to_Rosetta}/main/source/bin/FlexPepDocking.linuxgccrelease \
      -database {path_to_Rosetta}/main/database \
      -in:file:s start_0001.pdb -native native.pdb \
      -pep_refine -ex1 -ex2aro -use_input_sc -nstruct 10
```