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

Calculated in PeptiDerive

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

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](http://rosie.rosettacommons.org/peptiderive)
   • Necessary input: PDB of protein-protein complex
   • Output: Protein-peptide complex

   Identify peptides that can compete

2. Redock Output Peptide-Protein Complex with FlexPepDock
   • [http://flexpepdock.furmanlab.cs.huji.ac.il/](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
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
FlexPepDock Server Output

For download:
- Top 10 model pdb and scores

Check for large movement of peptides here

Score vs RMSD of all 200 poses
FlexPepDock Server Output

For download:
- Top 10 model pdb files and scores

Score vs RMSD of all 200 poses

Check for large movement of peptides here
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
```