Protein-Protein Docking in Rosetta

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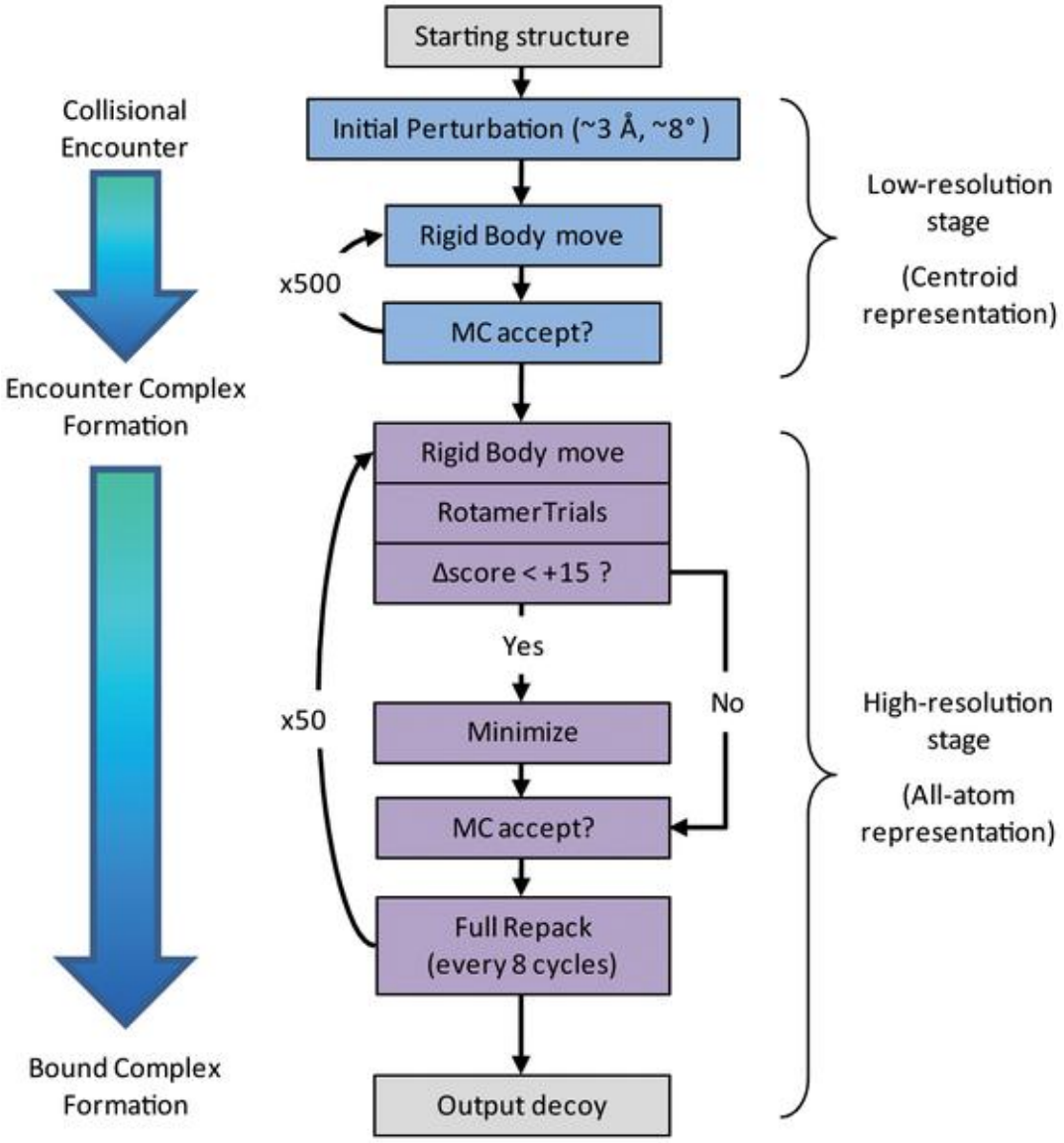
ROSETTA Workshop
April 27, 2017

Overview - Protein Docking



- Mimics natural process of protein interaction
- Centroid-based coarse grain stage
- Fine conformational search with side chain flexibility

- Hints:
  - Incorporate experimental data to decrease conformational search space

Chaudhury *et al*, PlosONE, 2011

General Docking Protocol

Prepare input files

- Input structures
- RosettaScripts XML File
- Options File

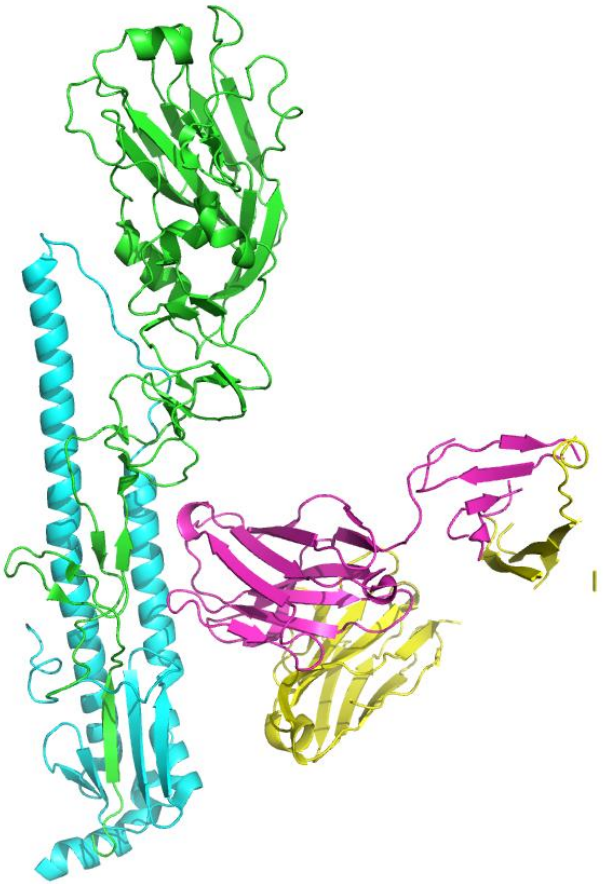
Perform docking calculations

Analyze results

- Plot Score vs. RMSD
- Examine interface character

Example System: Influenza Hemagglutinin bound by mAb CR6261

- Crystallized both in complex with H1 and H5 hemagglutinin (HA)
- Cross-docking experiment – antibody from one PDB (3GBN) and HA from another (3GBM)
- Influenza H5 hemagglutinin
  - 2 chains: HA1, HA2
- CR6261
  - Human derived monoclonal antibody
  - 2 chains: Heavy and Light



Developing your docking XML file

Please open the docking_full.xml file

gedit ~/rosetta_workshop/tutorials/protein-protein_docking/docking/docking_full.xml

Where should you start?

```
<PROTOCOLS>
        <Add mover="dock_low"/>
        <Add mover="srsc" />
        <Add mover="dock_high" />
        <Add mover="minimize_interface" />
</PROTOCOLS>
```

Docking movers

```
<Docking name="string" score_low=(string) score_high=(string)
fullatom=(bool) local_refine=(bool) jumps=(Integer vector)
optimize_fold_tree=(bool) conserve_foldtree=(bool) design=(bool)
ignore_default_docking_task=(bool) task_operations=(comma-separated list)/>
```

- score_low: scorefxn for centroid-level docking
- score_high: scorefxn for full atom docking
- fullatom: if true, do full atom docking
- local_refine: if true, skip centroid.
- jumps: where should we carry out rigid body motions (not used here)
- optimize_fold_tree: should DockingProtocol make the fold tree for this pose
- conserve_foldtree: should DockingProtocol reset the fold tree to the input one after it is done
- design: interface design for all chains downstream of the rb_jump
- ignore_default_docking_task: allows you to ignore the default docking task and only use the ones defined in your task_operations section

Docking movers

```
<PROTOCOLS>
                <Add mover="dock_low"/>
                <Add mover="srsc" />
                <Add mover="dock_high" />
                <Add mover="minimize_interface" />
</PROTOCOLS>
```

```
<Docking name="dock_low" score_low="score_docking_low"
score_high="talaris2014" fullatom="0" local_refine="0"
optimize_fold_tree="1" conserve_foldtree="0" ignore_default_docking_task="0"
design="0" task_operations="ifcl,prfrp" jumps="1"/>

<Docking name="dock_high" score_low="score_docking_low"
score_high="talaris2014" fullatom="1" local_refine="1"
optimize_fold_tree="1" conserve_foldtree="0" design="0"
task_operations="ifcl,prfrp" jumps="1"/>
```

```
<SaveAndRetrieveSidechains name="srsc" allsc="0" /> Speeds the move from
centroid to full atom mode
```

Important options

-docking:partners AB_HL # sets rigid body docking partners – chains must be in this order in the PDB

-docking:randomize1 # randomize the first docking partner – should be passed to run global docking (not used in this tutorial)

-docking:dock_pert 3 8 # set coarse perturbation parameters (degrees and angstroms)

-docking:dock_mcm_trans_magnitude 0.1 # refinement translational perturbation

-docking:dock_mcm_rot_magnitude 5.0 # refinement rotational perturbation

TaskOperations

```
<TASKOPERATIONS>
    <InitializeFromCommandline name="ifcl"/>
    <RestrictToRepacking name="rtr" />

    <RestrictToInterfaceVector name="rtiv" chain1_num="1,2"
chain2_num="3,4" CB_dist_cutoff="10.0" nearby_atom_cutoff="5.5"
vector_angle_cutoff="75" vector_dist_cutoff="9.0" />

    <PreventResiduesFromRepacking name="prfrp"
residues="11,41,345" />

</TASKOPERATIONS>
```

Minimization movers

Use a single round of FastRelax to refine the backbone of both docking partners

<FastRelax name="minimize_interface" scorefxn="talaris2014" repeats="1" task_operations="ifcl,rtr,rtiv,prfrp" />

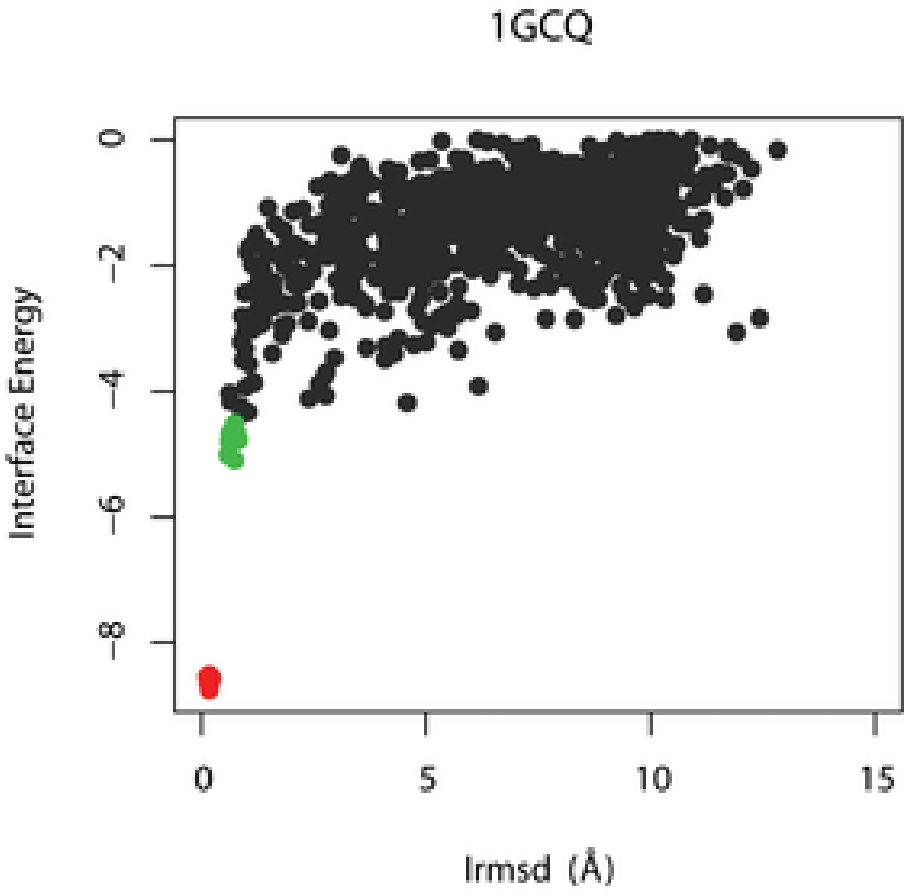
- Restrict to repacking – default behavior is design (very important)
- Interface from command line – allows the mover to read options from the command line

Perform analysis

- Score vs. RMSD plots to identify a docking funnel
  - In experimental studies, the 'native structure' is a good scoring structure, one that fulfills experimental restraints, or a cluster center
- It may be necessary to cluster and dock again, using the top cluster centers as starting templates. This will help to drive the models into an energy well. The 'correct' model will continue down into an energy well while incorrect models will stall.
- Look at the structures
  - Unsatisfied polar residues
  - Binding density
  - Average Degree of Residue Burial

Fleishman, S. J.; Baker, D., Role of the biomolecular energy gap in protein design, structure, and evolution. *Cell* **2012,** *149* (2), 262-73
Fleishman, S. J.; Whitehead, T. A.; Strauch, E. M.; Corn, J. E.; … ; Baker, D., Community-wide assessment of protein-interface modeling suggests improvements to design methodology. *Journal of molecular biology* **2011,** *414* (2), 289-302.

Score vs. RMSD plots – identifying a docking funnel



- Key features:
  - Native complex is kept at low RMSD, low scoring
  - Good models are sampled (< 2 A RMSD)
  - Score function distinguishes between low and high RMSD models

Gray – Full docking protocol
Green – Refinement only
Red – Native complex refined

Today's Tutorial

```
cd
~/rosetta_workshop/tutorials/protei
n-protein_docking/

firefox protein-
protein_docking_tutorial.html
```

Reference List

- **Docking**
  - Gray, J. J.; Moughon, S.; Wang, C.; Schueler-Furman, O.; Kuhlman, B.; Rohl, C. A.; Baker, D., Protein-protein docking with simultaneous optimization of rigid-body displacement and side-chain conformations. *Journal of molecular biology* **2003,** *331* (1), 281-99.
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  - Chaudhury, S.; Sircar, A.; Sivasubramanian, A.; Berrondo, M.; Gray, J. J., Incorporating biochemical information and backbone flexibility in RosettaDock for CAPRI rounds 6-12. *Proteins* **2007,** *69* (4), 793-800.
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  - Sivasubramanian, A.; Sircar, A.; Chaudhury, S.; Gray, J. J., Toward high-resolution homology modeling of antibody Fv regions and application to antibody-antigen docking. *Proteins* **2009,** *74* (2), 497-514.
  - Sircar, A.; Gray, J. J., SnugDock: paratope structural optimization during antibody-antigen docking compensates for errors in antibody homology models. *PLoS computational biology* **2010,** *6* (1), e1000644

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- **Design**
  - Fleishman, S. J.; Whitehead, T. A.; Ekiert, D. C.; Dreyfus, C.; Corn, J. E.; Strauch, E. M.; Wilson, I. A.; Baker, D., Computational design of proteins targeting the conserved stem region of influenza hemagglutinin. *Science* **2011,** *332* (6031), 816-21.
  - Fleishman, S. J.; Corn, J. E.; Strauch, E. M.; Whitehead, T. A.; Karanicolas, J.; Baker, D., Hotspot-centric de novo design of protein binders. *Journal of molecular biology* **2011,** *413* (5), 1047-62.
  - Der, B. S.; Machius, M.; Miley, M. J.; Mills, J. L.; Szyperski, T.; Kuhlman, B., Metal-mediated affinity and orientation specificity in a computationally designed protein homodimer. *Journal of the American Chemical Society* **2012,** *134* (1), 375-85.
  - Mandell, D. J.; Kortemme, T., Computer-aided design of functional protein interactions. *Nature chemical biology* **2009,** *5* (11), 797-807.
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- **Analysis**
  - Fleishman, S. J.; Baker, D., Role of the biomolecular energy gap in protein design, structure, and evolution. *Cell* **2012,** *149* (2), 262-73.
  - Fleishman, S. J.; Khare, S. D.; Koga, N.; Baker, D., Restricted sidechain plasticity in the structures of native proteins and complexes. *Protein science : a publication of the Protein Society* **2011,** *20* (4), 753-7.
  - Fleishman, S. J.; Whitehead, T. A.; Strauch, E. M.; Corn, J. E.; … ; Baker, D., Community-wide assessment of protein-interface modeling suggests improvements to design methodology. *Journal of molecular biology* **2011,** *414* (2), 289-302.