Protein-Protein Docking –
Current Methods and New Challenges

Dave Ritchie
Team Orpailleur
Inria Nancy – Grand Est

Outline

Review of Selected CAPRI Targets
Some Algorithms Used in CAPRI
Assembling Symmetric Multimers
Hybrid Approaches – Knowledge-Based + MD
New Challenges – Structural Systems Biology
New Challenges – Modeling Large Molecular Machines

Protein Docking – A Molecular Recognition Problem

- A six-dimensional puzzle – do these proteins fit together?
- Yes, they fit!
- It is mostly a rotational problem: ONE translation plus FIVE rotations...
- But proteins are flexible => multi-dimensional space!
- So, how to calculate whether two proteins recognise each other?

The CAPRI Blind Docking Experiment

- CAPRI = Critical Assessment of PRedicted Interactions
- http://www.ebi.ac.uk/msd-srv/capri/
- Given the unbound structure, predict the unpublished 3D complex...
- T8 = nidogen/laminin
- T9 = LiCT dimer
- T10 = TEV trimer
- T11-12 = cohesin/dockerin
- T13 = Fab/SAG1
- T14 = PP1δ/MYPT1
- T15 = colicin/ImmD
- T16 = Fab/bovine prion
- T18 = Xylanase/TAXI
- T19 = Fab/bovine prion
- T11, T14, T19 involved homology model-building step...
- T15-T17 cancelled: solutions were on-line & found by Google!!
CAPRI Target T6 Was A Relatively Easy Target
- AMD9 (camel antibody) / Amylase (pig)
- Little difference between unbound & bound conformations
- Classic binding mode: antibody loops blocking the enzyme active site
- Several CAPRI groups made “high accuracy” models (RMSD ≤ 1Å)

CAPRI Target T27 Was A Surprisingly Difficult Target
- Arf6 GTPase / LZ2 Leucine zipper was difficult for most predictors
  - http://www.ebi.ac.uk/msd-srv/capri/
  - Circles show LZ2 centres:
    - blue = high quality
    - green = medium quality
    - cyan = acceptable quality
    - yellow = wrong

Predicting Protein-Protein Binding Sites
- Many algorithms/servers exist for predicting protein binding sites
  - For a review: Fernández-Recio (2011), WIREs Comp Mol Sci 1, 680–698
- Many docking algorithms show clusters of orientations – docking “funnels”
- Lensink & Wodak: docking methods are best predictors of binding sites
  - Fernández-Recio, Abagyan (2004), J Molecular Biology, 335, 843–865
  - Lensink, Wodak (2010), Proteins, 78, 3085–3095

CAPRI Results: Targets 8 – 19

<table>
<thead>
<tr>
<th>Software</th>
<th>T8</th>
<th>T9</th>
<th>T10</th>
<th>T11</th>
<th>T12</th>
<th>T13</th>
<th>T14</th>
<th>T18</th>
<th>T19</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICM</td>
<td>**</td>
<td>*</td>
<td>**</td>
<td>***</td>
<td>*</td>
<td>***</td>
<td>*</td>
<td>***</td>
<td>**</td>
</tr>
<tr>
<td>PatchDock</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>***</td>
<td>*</td>
<td>***</td>
<td>**</td>
<td>*</td>
</tr>
<tr>
<td>ZDOCK/RDOCK</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>**</td>
<td>*</td>
</tr>
<tr>
<td>FTDock</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>**</td>
<td>*</td>
</tr>
<tr>
<td>RosettaDock</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SmoothDock</td>
<td>**</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RosettaDock</td>
<td>***</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Haddock</td>
<td>***</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ClusPro</td>
<td>**</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3D-DOCK</td>
<td>**</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MolFit</td>
<td>***</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hex</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Zhou</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DOT</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ATTRACT</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Valencia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GRAMM</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Umeayama</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kaznessis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fano</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

ICM Docking – Multi-Start Pseudo-Brownian Search

- Start by sticking pins in protein surfaces at 15 Å intervals
- For each pair of pins, find minimum energy (6 rotations for each):
  \[ E = E_{HVW} + E_{CVW} + 2.16E_{el} + 2.53E_{hb} + 4.35E_{hp} + 0.20E_{solv} \]

- Often gives good results, but is computationally expensive

Fernández-Recio, Abagyan (2004), J Mol Biol, 335, 843–865

PatchDock – Docking by Geometric Hashing

- Use “MS” program to calculate mesh surfaces for each protein
- Divide the mesh into convex "caps", concave "pits", and flat "belts"
- For docking, match pairs of concave/convex, and flat/any ...
- ... then test for steric clashes between rest of surfaces
- The method is fast (minutes/seconds), and gave good results in CAPRI

Duhovny et al. (2002), LNCS 2452, 185–200
Schneidman-Duhovny et al. (2005), NAR, 33, W363–W367
Connolly (1983), J Appl Cryst, 16, 548–558

Protein Docking Using Fast Fourier Transforms

- Conventional approaches digitise proteins into 3D Cartesian grids...
  - ...and use FFTs to calculated TRANSLATIONAL correlations:
    \[ C[\Delta x, \Delta y, \Delta z] = \sum_{x,y,z} A[x,y,z] \times B[x + \Delta x, y + \Delta y, z + \Delta z] \]

- BUT for docking, have to repeat for many rotations – expensive!
- Conventional grid-based FFT docking = SEVERAL CPU-HOURS

Katchalski-Katzir et al. (1992) PNAS, 89 2195–2199

Quick Summary of FFT Docking Methods

3D Cartesian FFT Methods
- DOT (shape + electro): http://www.sdsc.edu/CCMS/DOT/
- FTDOCK (shape + electro) http://www.sbg.bio.ic.ac.uk/docking/
- GRAMM (shape?) http://vakser.bioinformatics.ku.edu/main/resources_gramm.php
- ZDOCK (shape + “ACP”) http://zdock.umassmed.edu/software/
- PIPER (shape + “DARS” potential): http://cluspro.bu.edu/
- MegaDock (shape only?): http://www.bi.cs.titech.ac.jp/megadock/

Polar Fourier FFT Methods
- Hex (shape + electro): http://hex.loria.fr/
- Frodock (shape only?): http://chaconlab.org/methods/docking/frodock/

Interactive FFT with 3D Graphics
- Hex!
Knowledge-Based Protein Docking Potentials

- Several groups have developed “statistical potentials”

- Define interaction energy (“inverse Boltzmann”):
  \[ E_{IJ} = -RT \ln \left( \frac{P_{nat}^{IJ}}{P_{ref}^{IJ}} \right) \]
  
  \( P_{nat}^{IJ} \) = prob. that atoms I and J are in contact in native complex
  
  \( P_{ref}^{IJ} \) = reference state prob., calculated from 20,000 docking decoys

- This gives a matrix of 18 x 18 atom-type interaction energies
  
  - Clever trick: diagonalise matrix to get first 4 or 6 leading terms...
  
  - ... allows PIPER to use 4 or 6 FFTs instead of 18

- PIPER + DARS is one of the best approaches in CAPRI...


Consider Protein Docking in Polar Coordinates

- Rigid docking can be considered as a largely ROTATIONAL problem
- This means we should use ANGULAR coordinate systems

- With FIVE rotations, we should get a good speed-up?

Spherical Harmonic Molecular Surfaces

- Use spherical harmonics (SHs) as orthogonal shape “building blocks”
  
  - Reals SHs \( y_{lm}(\theta, \phi) \), and coefficients \( a_{lm} \)
  
  - Encode distance from origin as SH series:
    \[ r(\theta, \phi) = \sum_{l=0}^{L} \sum_{m=-l}^{l} a_{lm} y_{lm}(\theta, \phi) \]

  - Calculate coefficients by numerical integration

  - Good for shape-matching, not so good for docking...

  Ritchie and Kemp (1999), J. Comp. Chem. 20, 383–395
Docking Needs 3D Polar Fourier Representation

- Special orthonormal Laguerre-Gaussian radial functions, $R_n(r)$
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
}
Exploiting Prior Knowledge in SPF Docking

- Knowing just one key residue can reduce search space enormously...
- This accelerates calculation and helps to reduce false-positives...

Docking Very Large Molecules Using Multi-Sampling

- Example: docking an antibody to the VP2 viral surface protein

HexServer – GPU-Accelerated Web Server

- Very fast – can cover 6D search space using 1D, 3D, or 5D FFTs...
- “Easy” to accelerate the 1D FFTs on highly parallel GPUs ...
- Widely used around the world – 33,000 downloads...


RosettaDock – Flexible Side Chain Re-Packing

- Given a rigid body starting pose, repeat 50 times:
  - REMOVE and RE-BUILD side chains
  - Minimise as rigid-body with Monte-Carlo accept/reject

- Successful on several CAPRI targets and 50% of Docking Benchmark v2
Haddock – “Highly Ambiguous Data-Driven Docking”
- Flexible refinement using CNS with ambiguous interaction restraints (AIRs)
- Use of “active” and “passive” residues ensures active residues at interface
- E.g. residue $i$ of protein A:
  \[
  d_{\text{eff}}^{\text{iAB}} = (\sum_{m=1}^{N_A} \sum_{k=1}^{N_B} \frac{1}{d_{\text{ref}}^{\text{mA}}})^{-1/6}
  \]
- Restraints from:
  - SAXS
  - mutagenesis
  - mass spec
  - NMR

van Dijk et al. (2005) FEBS J, 272, 293–312
van Dijk et al. (2005) Proteins, 60, 232–238

Modeling Protein Flexibility Using Elastic Network Models
- ENMs assume protein $C_\alpha$ atoms are coupled via a harmonic potential
  \[
  V = \frac{1}{2} \sum_{i<j} C (d_{ij} - d_{ij}^0)^2
  \]
  \[
  H = (\partial/\partial x_i)(\partial/\partial x_j) V
  \]
- Then, represent protein as a linear combination of first eigenvectors:
  \[
  P^{\text{NEW}} = P_0 + \sum_{k=1}^{3N} w_k e_k
  \]
- On-line examples:
  - EINémo web-server: http://www.igs.cnrs-mrs.fr/elnemo/
  - Macromolecular Movements: http://www.molmovdb.org/

Andrusier et al. (2008), Proteins, 73, 271–289 (review)

Simulating Flexibility Using “Essential Dynamics”
- Generate distance-constrained samples in CONCOORD, then apply PCA
  \[
  C_{ij} = \langle (x_i - \bar{x}_i)(x_j - \bar{x}_j) \rangle
  \]
  \[
  E = E \Lambda E^T
  \]
  \[
  P^{\text{NEW}} = P^2 + \sum_{k=1}^{3N} \alpha_k e_k
  \]
- First eigenvectors encode most of RMSD between bound and unbound
- See also SwarmDock – http://bmm.cancerresearchuk.org/~SwarmDock/

Mustard, Ritchie (2005), Proteins 60, 269–274 (first NMA protein docking?)

EigenHex – Flexible Docking Using Pose-Dependent ENM
- Apply fresh eigenvector analysis to the top 1,000 Hex orientations

Overall approach:
- $C_\alpha$, elastic network model (ENM)
- Use up to 20 eigenvectors
- Search using PSO
- Score using DARS potential

Results:
- DARS works well but...
- Still need better scoring function
- Much effort – small improvement!!

Venkatraman, Ritchie (2012), Proteins, 80, 2262–2274
Docking Symmetric Structures

Several groups have developed symmetry docking algorithms

- Molfit ($D_2$): Berchanski et al. (2003), Proteins, 53, 817–829
- M-ZDOCK ($C_n$): Pierce et al. (2005), Bioinformatics, 21, 1472–1478
- SymmDock ($C_n$): Schneidman et al. (2005), Proteins, 60, 224–231
- Cluspro ($C_n, D_2, D_3$): Comeau et al. (2005), JSB, 150, 233-244

(These algorithms “post-filter” blind docking searches)

Symmetric complexes are remarkably common in the PDB

<table>
<thead>
<tr>
<th>n</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cn</td>
<td>8740</td>
<td>992</td>
<td>223</td>
<td>107</td>
<td>76</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>Dn</td>
<td>2111</td>
<td>585</td>
<td>173</td>
<td>46</td>
<td>20</td>
<td>23</td>
<td>6</td>
</tr>
</tbody>
</table>

(Data from: http://www.3dcomplex.org)

FFT-Based Symmetry Assembly

Illustration of $D_3$ symmetry

Symmetry Docking Operators

- We developed a simple operator notation for symmetry docking

$$\hat{T}(0, y, 0) \hat{R}(\alpha, \beta, \gamma) A(x) \longleftrightarrow \hat{R}(0, 0, \omega) \hat{T}(0, y, 0) \hat{R}(\alpha, \beta, \gamma) B(x)$$

- This allows 4D space to be expressed as polar Fourier expansions

Ritchie and Grudinin (2013), JOBIM Proceedings

Coming Soon: “SAM” – Symmetry Assembler

Uses multiple 1D Polar Fourier FFT searches

- Implemented for all point group symmetries: $C_n, D_n, T, O, I$
- Works well for small protein domains...

- Need to develop coarse-grained scoring for large proteins
- Need to extend to symmetric cryo-EM density fitting...

Systems Biology View of Protein-Protein Interactions

Protein interactions are central to many biological systems

Each protein is part of a large network of interactions

- To understand how proteins really work, we need to know their three-dimensional structures... But solving structures is difficult!
- We need to exploit knowledge of known structures and interactions...
Protein-Protein Interaction Challenges

- Can we predict all interactions within a proteome – the interactome?
- For each interaction, can we predict the interface and 3D complex?
- For each protein can we predict its ligand binding sites?


Protein-Protein Interaction Resources

- STRING – Search Tool for Retrieval of Interacting Genes
  - 12 million known PPIs; 44 million predicted – http://string.embl.de/
- 3DID – 160,000 DDIs – http://3did.irbbarcelona.org/
- KBDOCK – Knowledge-Based Docking (“Domain Family Binding Sites”)
  - 280,000 DDIs + 4,000 DFBIs – http://kbdock.loria.fr/

Szklarzyk et al. (2011), Nucleic Acids Research, 39, D561–D568
Stein et al. (2010), Nucleic Acids Research, 33, D413–D417
Ghoorah et al. (2014), Nucleic Acids Research, 42, D389–D395

The Need for a Structural Classification of DDIs

- Pfam classifies sequences into domain families
- Families of similar sequences often have similar structures
- CATH and SCOP classify structures into structural families
- KBDOCK introduces domain family binding sites (DFBSs)

Superposing DDIs in 3D Space – E.g. Kunitz BPTI

For each Pfam domain family:
- Place all members and their interaction partners in a common frame
- Use conserved residue positions to guide structural alignment
- This reveals the overall spatial distribution
KBDOCK Statistics

**PDB**
- Protein Data Bank - ∼ 85,000 protein structures (June 2013 snapshot)

**Pfam**
- Database of protein domain families
- Uses multiple sequence alignments to define domains
- Based on UniProt database
- Contains 14,831 domain families
- Of which, 6,516 have 3D structures in the PDB

**KBDOCK**
- Uses Pfam to define domains
- Extracts all DDIs from PDB files
- Some statistics:
  - 231,405 PDB total chains
  - 288,309 total domains
  - 239,494 total DDIs
  - 12,498 inter-chain homo DFBSs
  - 4,001 inter-chain hetero DFBSs
  - 3,021 intra-chain hetero DFBSs
  - 745 intra-chain homo DFBSs
  - 1,213 domain-peptide interactions

The KBDOCK Database and Web Server
- Domains are superposed and clustered by PFAM family
- ∼ 8,000 non-redundant domain family binding sites (DFBSs)
- ∼ 20,000 domain family interactions (DFIs)
- http://kbdock.loria.fr/

The Inside of a Cell is Highly Crowded
- This image shows a model of the cytoplasm in *E. Coli*
- Can we use docking algorithms to predict the protein-protein interactions?
  - McGuffee, Elcock (2009), PLoS Comp Biol, 6, e1000694

Large-Scale Cross-Docking Using Hex
- Wass et al. cross-docked 56 true pairs with 922 non-redundant “decoys”
- For each pair, they plotted the profile of the best 20,000 docking scores...
- (-ve scores are good; red/blue = correct PPI; red/cyan = incorrect interactions)
  - 48/56 true PPIs have significantly higher energies than false pairs
  - Only 8/56 true PPIs have indistinguishable profiles to the non-binders
  - Wass et al. (2011) Molecular Systems Biology, 7, article 469
**IMP – Integrative Modeling Platform**

- Python system for multi-component modeling – http://salilab.org/imp/
- Combines data from: cryoEM (mainly), X-Ray, NMR, SAXS, Modeller, ...
- ... with interaction data from BioGRID – http://thebiogrid.org/

Minimise multi-term objective function:

\[ F = \sum_i \alpha_i + \sum_{i<j} \beta_{ij} \]

- \( \alpha_i \) are single-body terms (e.g. density fitting score, protrusion penalty)
- \( \beta_{ij} \) are two-body terms (e.g. docking scores)

But it is a highly combinatorial search space, with missing/incomplete data...

Russel et al. (2012) PLoS Biology, 10, e1001244
Lasker et al. (2009) J Molecular Biology, 388, 180–194

**Putting The Pieces Together – The Nuclear Pore Complex**

- The NPC has some 650 components – raw data at http://salilab.orgnpc/

It required an immense multi-disciplinary effort to build this model ...

See Dreyfuss et al. for an interesting computational validation of the model

Dreyfuss et al. Proteins (2012) 80, 2125–2136

**Conclusions**

- (+) Better potentials are helping to improve pair-wise docking
- (+) Cross-docking can detect true partners remarkably often
- (+) General FFT symmetry assembly is “coming soon”...
- (−) Modeling protein flexibility during docking is still difficult
- (+) Knowledge-based protein docking is becoming very useful
  - Most Pfam families have just one binding site – often re-used
- (+) Current strategy: “data-driven” or “knowledge-based” docking
- (?) The next challenge – modeling “the structural interactome”
  - All-vs-all docking ?
  - Electron-microscopy density fitting ?
  - Assembling multi-component machines ?

**Acknowledgments**

Anisah Ghoorah
Matthieu Chavent
Diana Mustard
Vishwesh Venkatraman
Lazaros Mavridis
BBSRC, EPSRC, ANR
It was given that there were two different binding sites. We searched SCOPPI and 3DID for similar 3D interactions. This helped to identify two inhibitory loops on API-A.

Using Hex + MD refinement gave nine "acceptable" solutions.