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## **EROS-DOCK and EROS-DOCK MULTI-BODY Approach**

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Maria-Elisa Ruiz-Echartea, Isaure Chauvot de Beauchêne, David Ritchie. EROS-DOCK and EROS-DOCK MULTI-BODY Approach. CAPRI evaluation meeting, Apr 2019, Hinxton, United Kingdom. hal-02394484

**HAL Id: hal-02394484**

**<https://hal.science/hal-02394484>**

Submitted on 1 Sep 2020

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# EROS-DOCK

Exhaustive Protein-Protein Docking Using Branch-and-Bounds Rotational Search

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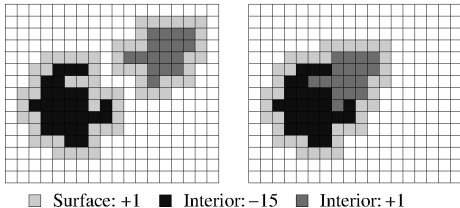
# Rigid Body Protein Docking Problem

- Involves sampling and scoring.
- 6 degrees of freedom.
- Docking remains as a challenging problem.



# Protein Docking Using Fast Fourier Transforms

- Conventional approaches digitise proteins into 3D Cartesian grids...

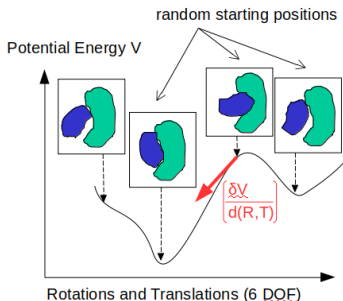
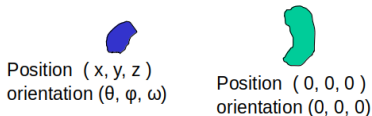


- ...and use FFTs to calculate TRANSLATIONAL correlations:

BUT for docking, have to REPEAT for many rotations.

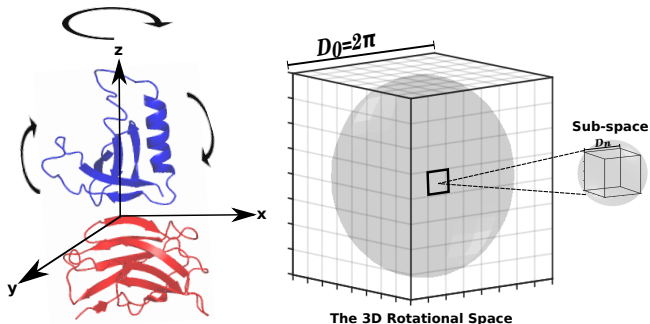
# Multiple Starting Positions and Minimizations

- Atomistic or “coarse-grained” (CG) representations.
- Monte-Carlo or gradient-based techniques to search local energy minima.



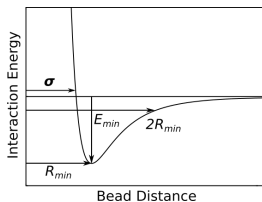
# A New Search Algorithm: EROS-DOCK

- The space 3D Euler angle rotations represented by a quaternion “ $\pi$ -ball”.
- Used previously for shape registration.
- Never used before for docking.



Hartley, Richard I., and Fredrik Kahl. "Global optimization through rotation space search." International Journal of Computer Vision 82.1 (2009): 64-79.

# Defining Initial Docking Contact Poses

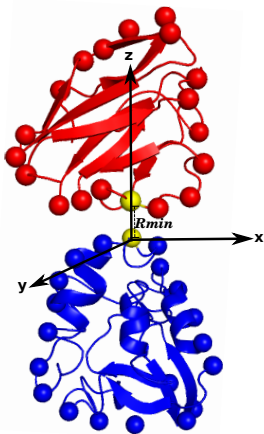


Complex	$d/\text{\AA}$	% of Complexes
Bound	$<0.10$	93
	$<0.23$	100
Unbound	$<0.10$	86
	$<0.20$	98

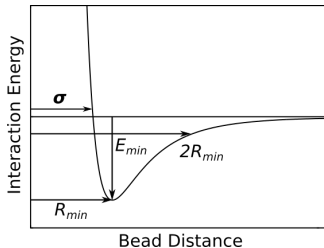
- CG representation

Zacharias, Martin. "Proteinprotein docking with a reduced protein model accounting for sidechain flexibility." Protein Science 12.6 (2003): 1271-1282.

# Defining Initial Docking Contact Poses



- Repeat for each pair...
- Ready to look for “clash rotations”...





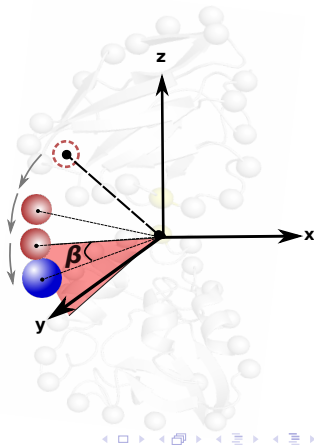
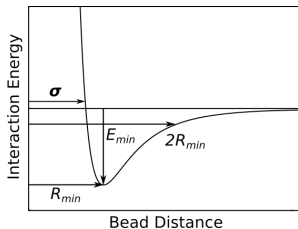
# Branch and Bounds Search using Bead Cone Angles

- Build a list of all possible “clash cone angles”.
- Repeat for each pair ...

If  $|R_a - L_b| > \sigma_{ab}$  then

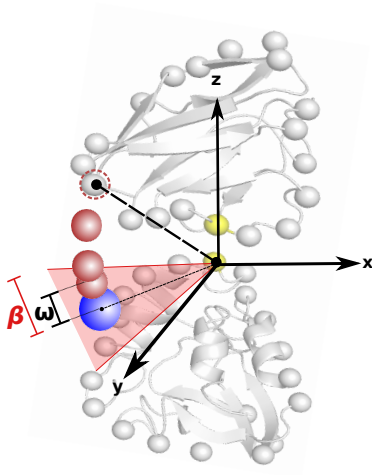
$a$  and  $b$  will never clash, else

$a$  and  $b$  will clash.



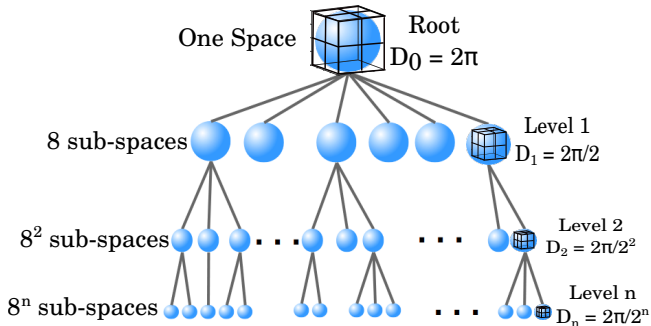
# Branch and Bounds Search using Bead Cone Angles

If  $\omega > \beta_{ab} + \Delta_s$   $s$  will never clash, else  $s$  will clash.



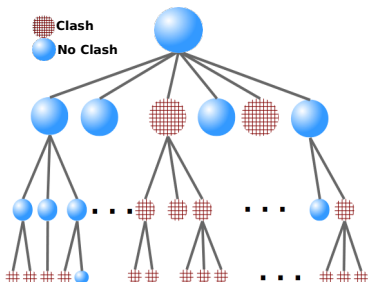
# Using the Quaternion $\pi$ -Ball

- Series of sample rotations dividing the  $\pi$ -ball into 8 cubes.
- The sample rotations represented as nodes in a 3D “search tree” data structure.
- Angular resolution 7.5 degrees.



# Coloring the Search Tree and Computation of Energies

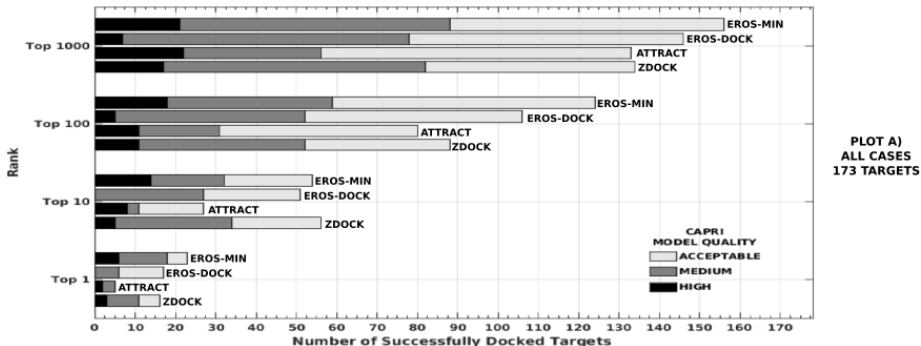
- First walk to identify spaces that lead to clash.
- Second walk to compute energies.



- On average 94% of the  $\pi$ -ball search space is pruned
- Only 6% of orientations are used to compute energies.

# Comparing EROS-DOCK With ATTRACT and ZDOCK

- 173 Docking Benchmark 4 target complexes.

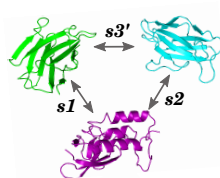
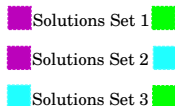


- EROS-MIN uses ATTRACT minimizations for a fair comparison.

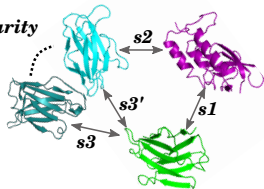
# EROS Multibody Docking

## The Approach

- All pairwise solutions.
- Combinatorial problem.
- Fast RMSD computational methods.



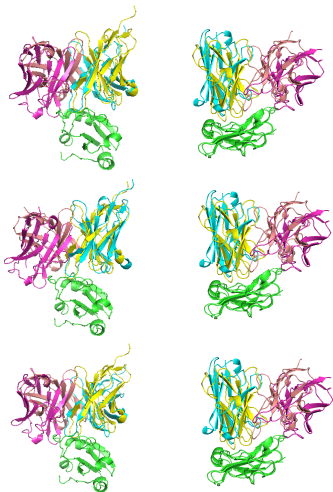
*Fast RMSD => Similarity Measure*



Petr Popov, Sergei Grudinin. Rapid determination of RMSDs corresponding to macromolecular rigid body motions. *Journal of Computational Chemistry*, Wiley, 2014, 35 (12), pp.950-956.

# EROS Multibody Docking

## The Approach



Complex	Energy Rank	Energy	Complex RMSD
1OAZ	526	-43.899	9.01
	3278	-43.16	7.56
	4290	-42.798	9.28
5NGV	409	-42.16	8.85
	799	-38.966	9.63
	989	-38.413	5.88

- The rank is not the best yet but . . .
- The algorithm is working correctly.

# Perspective

- The use of distance restraints to drive the docking.
- Improvement of the rank of good quality solutions of EROS-DOCK pairwise and multibody.
- Extend EROS-MULTIBODY to deal with a greater number of proteins.
- The use of other force fields.





thank you