Self assembly of protein subunits Negotiating the

Debnath Pal

Bioinformatics Centre

&

Supercomputer Education and Research Centre

Indian Institute of Science

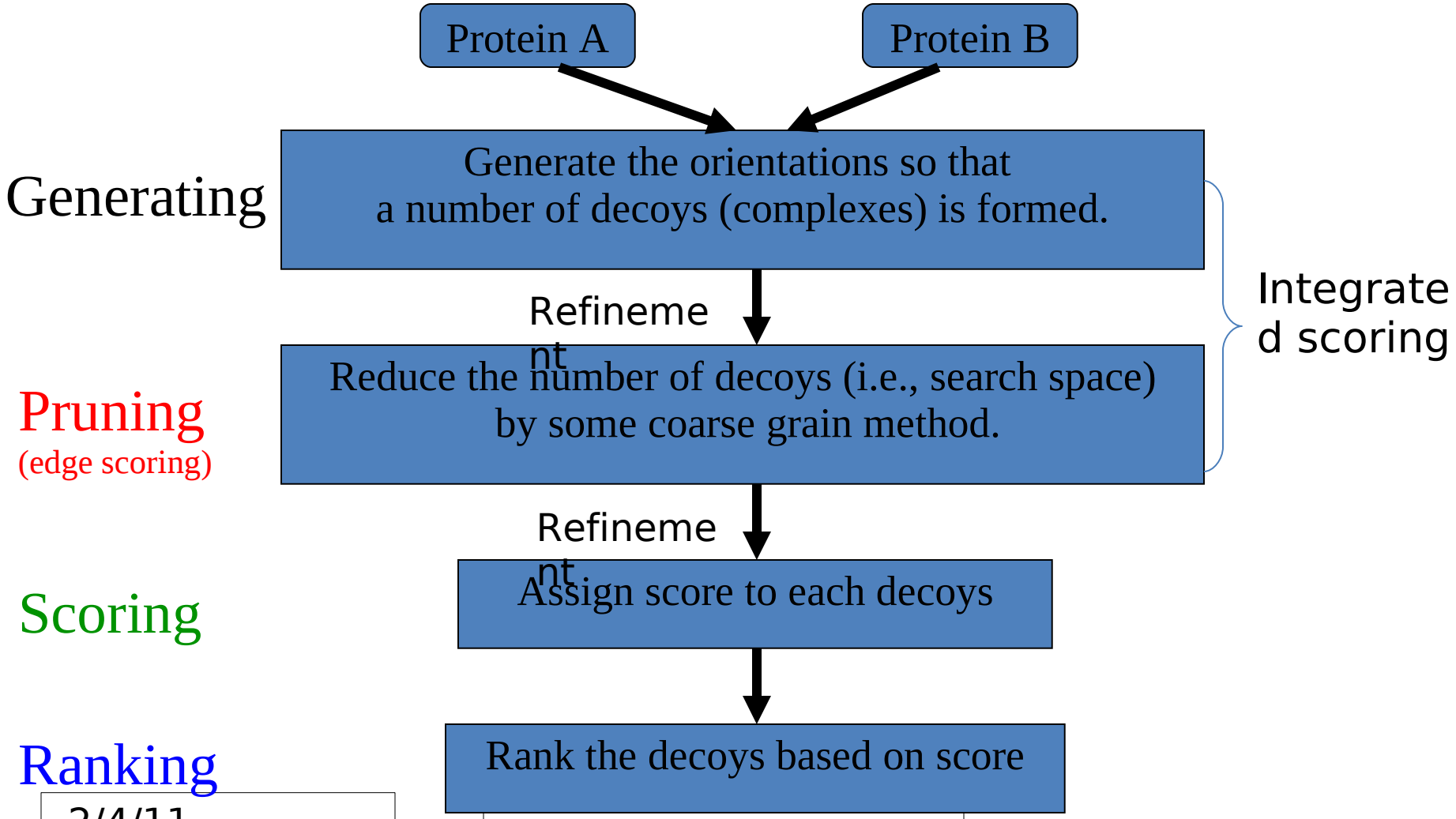
Bangalore 560 012

Click to edit Master subtitle style

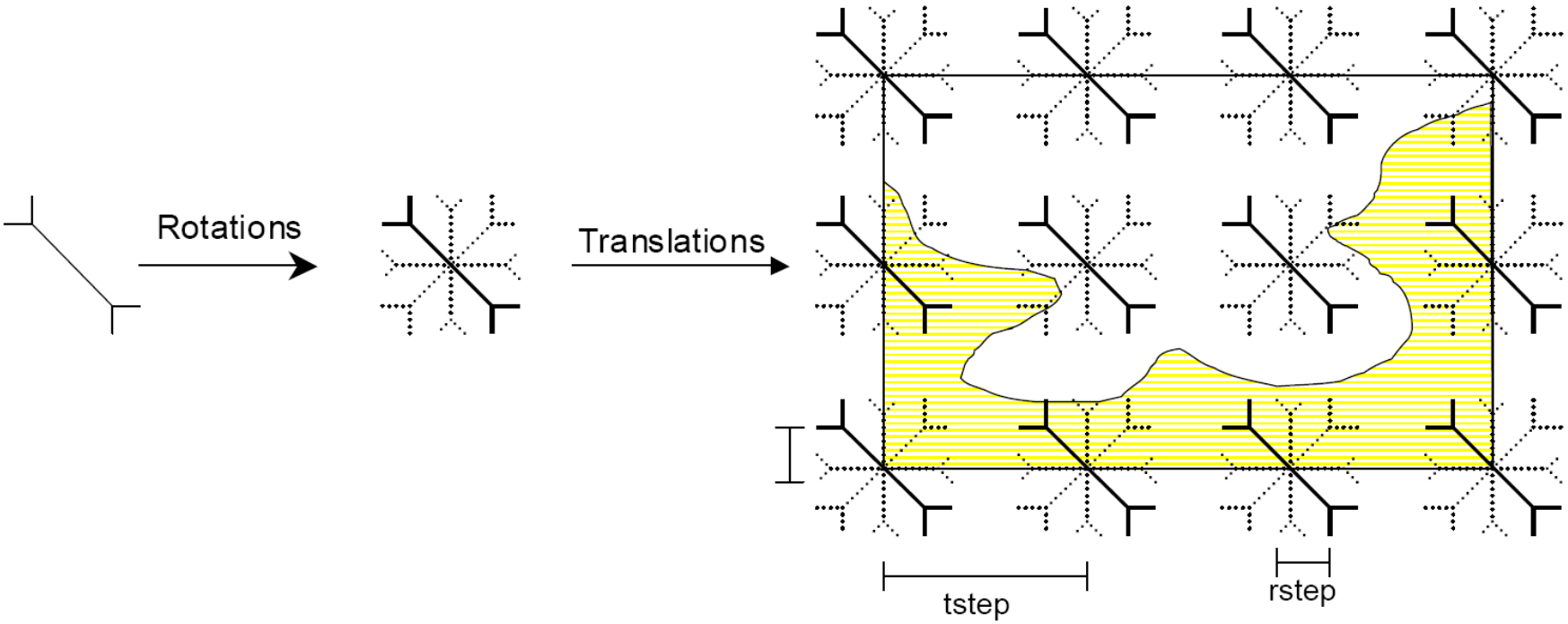
Supercomputer Education and Research Centre

Bioinformatics Centre

The Protein-Protein Docking



Decoy generation



The number of decoy generated increases with the density of rotation and translation

2/4/11

Their numbers could be from few thousands to more than

Pruning Decoy Set

- The number of docking “poses” obtained are anywhere between few thousand to few hundred thousand depending on the density of the docking search.
- Most of the docking poses in the sampling search are non native models and only a few are native-like.
- The number of decoys must be pruned to a manageable number on

Docking sampling and scoring

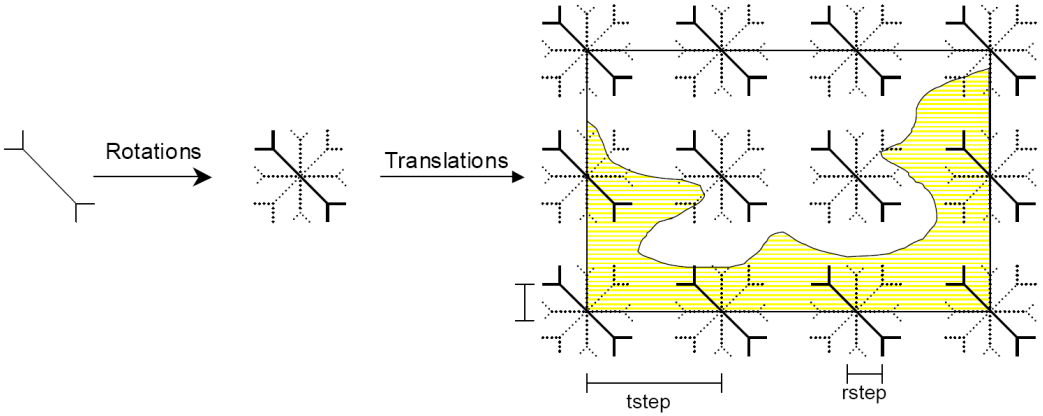
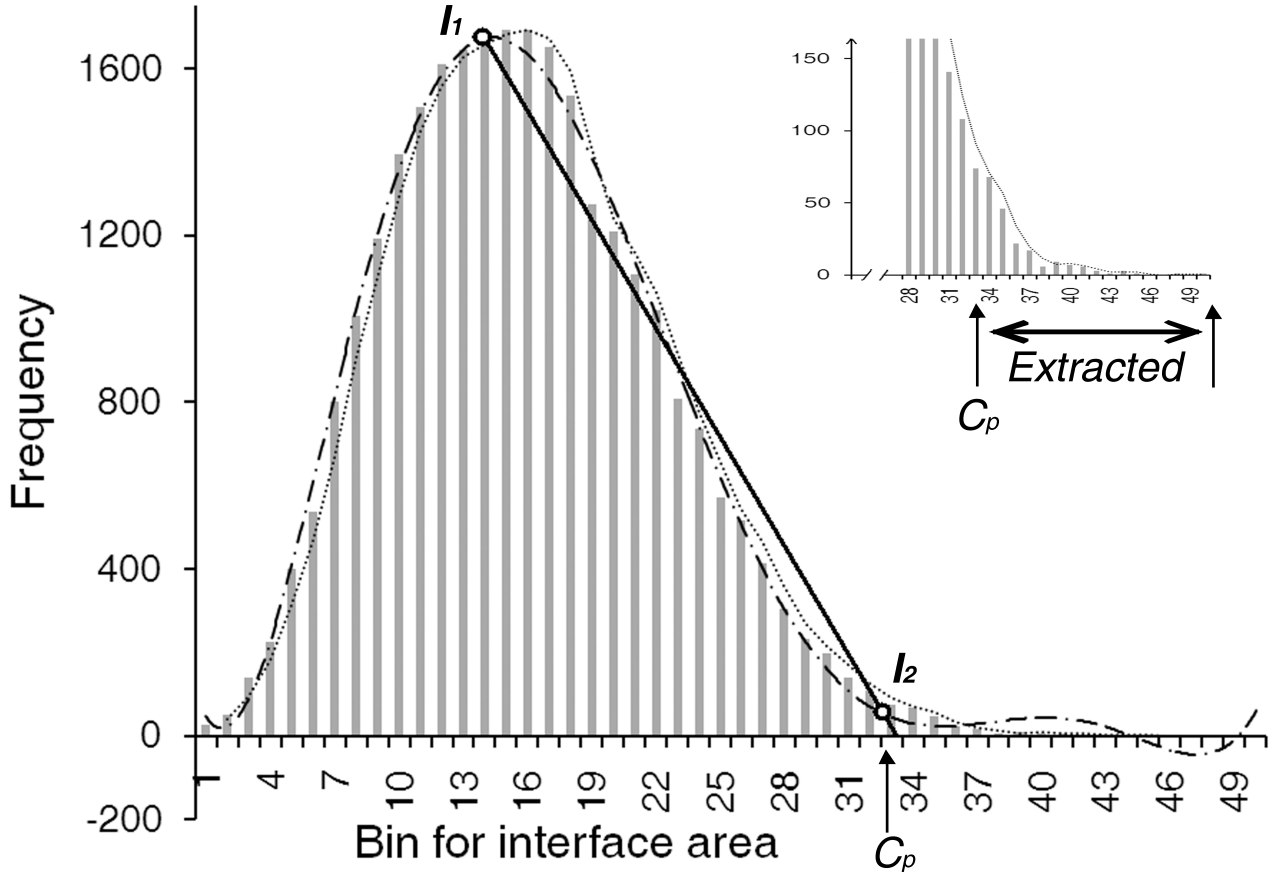


TABLE II. Classification of Docking Algorithms According to Function Parameters[†]

Algorithm name (reference)	Scoring stage in algorithm flow	Reference for the solution	Geometric complementarity	Hydrogen bonds	Contact area	Intramolecular overlap	Intermolecular overlap	Pairwise amino acid contacts	Electrostatic interactions	Solvation energy	Active site residues	Free energy
Sobolev et al.[241]	Integrated	Self	+	+	+	−	+	−	+	−	−	−
SP-DOCK Fradera et al.[186]	Edge	Known structure	+	+	−	+	+	−	+	−	−	−
SG-DOCK Fradera et al.[186]	Integrated	Known structure	+	+	−	+	+	−	+	−	−	−
Norel et al.[230]	Edge	Self	+	−	−	−	−	−	+	−	−	+
FTDOCK, Katchalski-Katzir et al.[142]	Edge	Self	+	−	−	−	−	−	−	−	−	−
Fischer 1995	Integrated	Self	+	−	−	−	+	−	−	−	−	−
DARWIN, Burnett and Taylor[34]	Integrated	Self	−	+	−	−	+	−	+	+	−	+
PUZZLE, Helmer-Citterich et al.[205]	Edge	Self	−	−	+	−	+	−	−	−	−	−
Hybrid algorithm, Hou et al.[242]	Integrated	Self	+	+	−	−	+	−	+	−	−	−
Gardiner et al.[77]	Integrated	Self	+	+	−	−	+	−	−	−	−	−
Jackson et al.[115]	Edge	Self	+	−	−	−	+	+	−	−	+	−
Norel et al.[40]	Edge	Self	+	−	−	−	+	−	+	−	−	−
ESCHER, Ausiello et al.[38]	Integrated	Self	+	+	−	−	+	−	+	−	−	−
Camacho et al.[148]	Integrative	Self	−	−	−	−	−	−	+	+	−	+
BiGGER, Palma et al.[113]	Integrative	Self	+	−	−	−	+	+	+	+	−	−

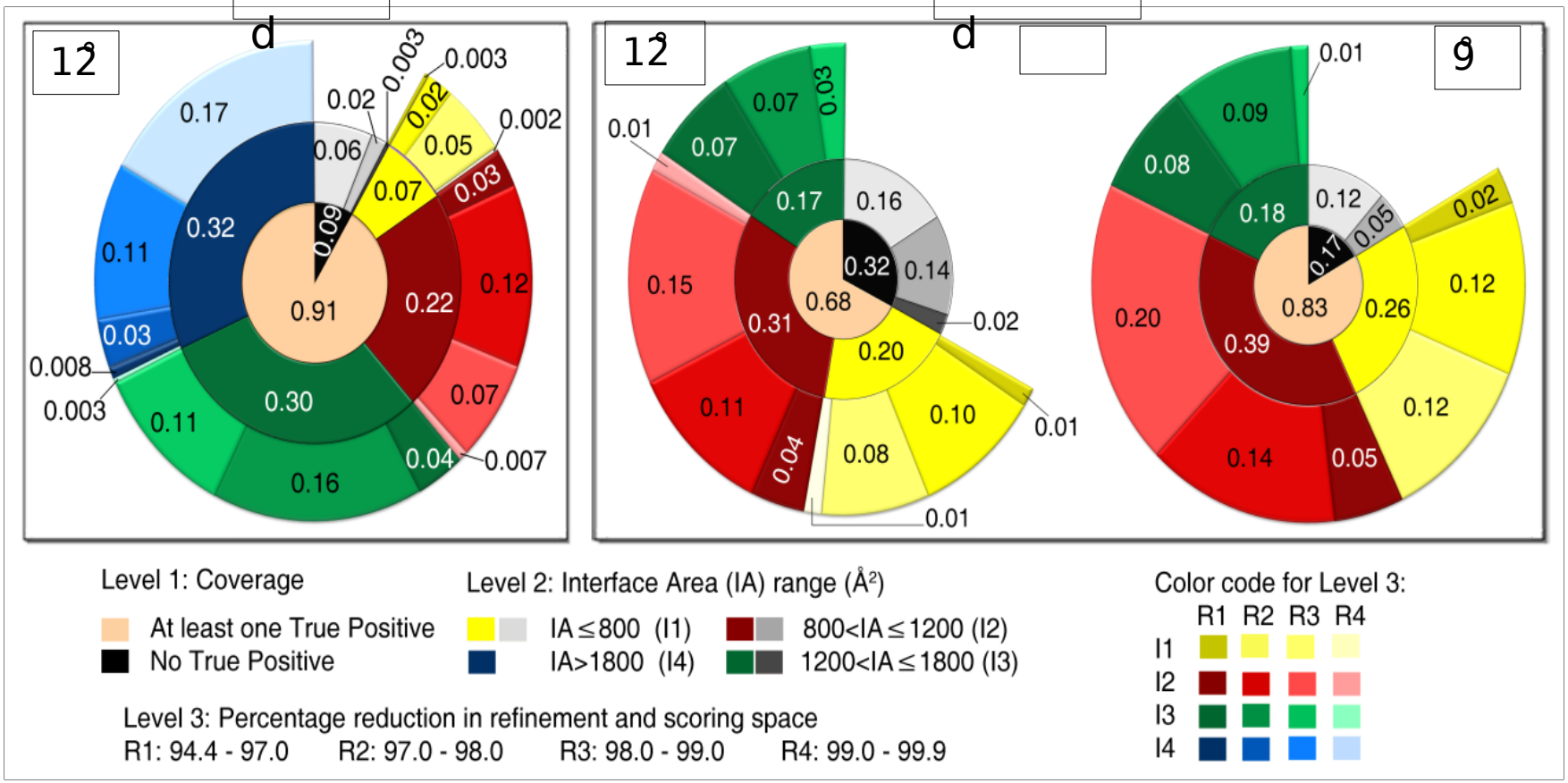
[†]Classification of some common algorithms according to the scoring function parameters they use, and the stage in the algorithm flow.

Rule-based pruning of docking decoys



Rule: native-like decoys have largest or near largest interface area

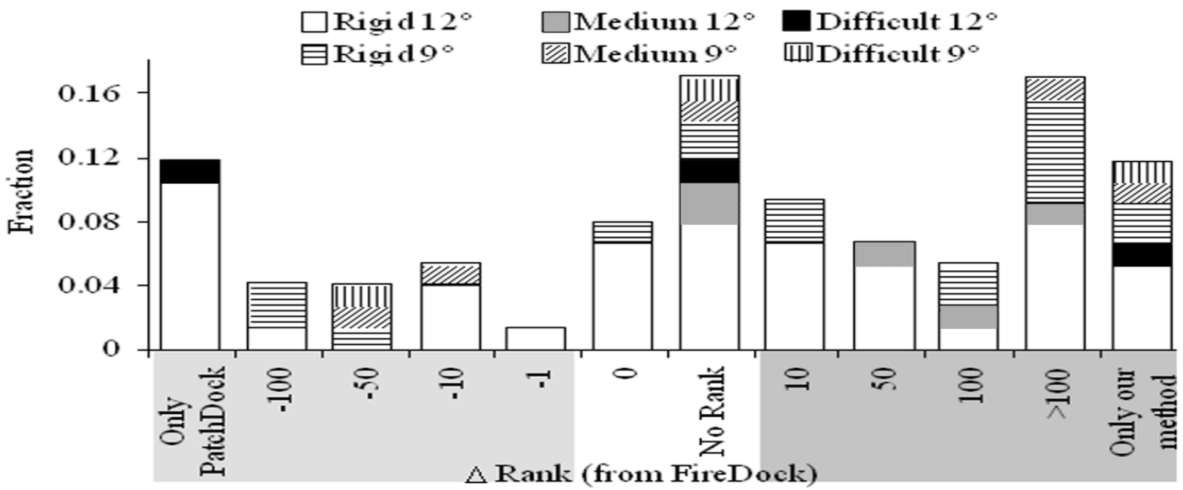
Rule-based pruning of docking decoys



Dataset: 922 bound, and 79 unbound binary docking targets (interface area: 193–7658 Å2). Bound target set: 822 homodimeric and 100 heterodimeric X-ray crystal structures, Resolution: ≤2.5 Å and R-factor: ≤0.2.

2/4/11

http://pallab.serc.iisc.ernet.in/prune



Docking gains

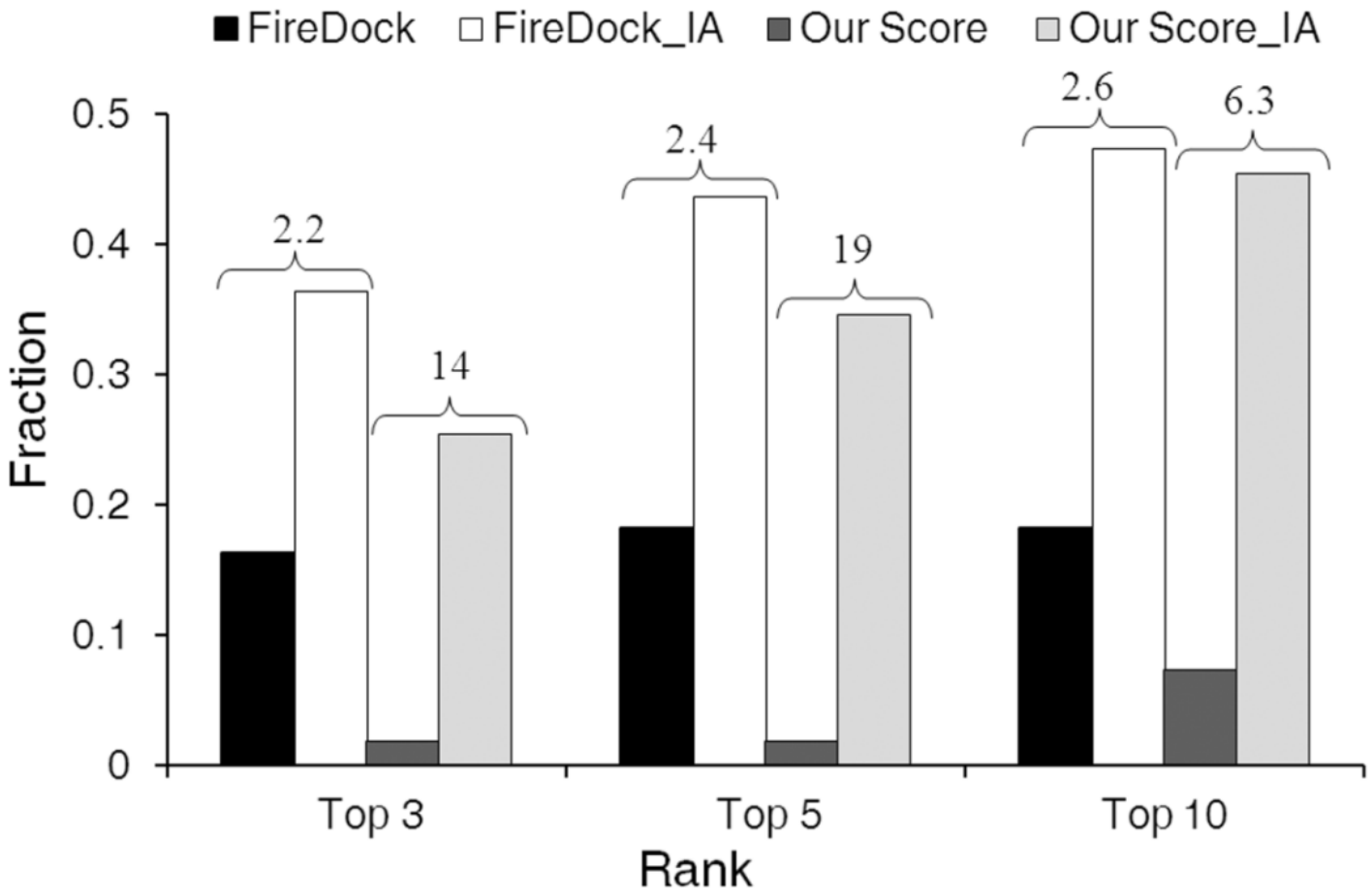
N = 55

Rotational Sampling Density Selection Rule:

If ((0.61 ≤ *MWr* ≤ 1.0) OR (*MWr* ≤ 0.6 AND *MWr* / *ASAr* < 0.75))
{12° sampling}
Else {9° sampling}

***MW* = Molecular weight**
***ASA* = Accessible surface area**
***r* = Ratio**

Docking gains benchmark



N =

2/4/11 55

http://pallab.serc.iisc.ernet.in/prune

Estimating geometric compatibility at protein-protein interface

Method		Pearson correlation coefficient					
		Complex				Monomer	Control
		Interface area range (Å²)					
		All	≤800	800< and ≤1500	>1500		
NIP	NSc	**0.95**	**0.79**	**0.85**	**0.91**	**0.88**	**0.96**
NIP	GVI	0.40	0.18	–0.08	0.16	0.07	0.39
NIP	C–NSc	**0.98**	**0.92**	0.91	**0.96**	**0.92**	**0.93**
NIP	NGC†	**0.66**	**0.70**	0.32	0.40	**0.83**	**0.75**
NSc	GVI	0.45	0.29	0.05	0.27	0.16	0.46
NSc	C–NSc	**0.95**	**0.75**	**0.81**	**0.93**	**0.83**	**0.90**
NSc	NGC†	**0.65**	**0.60**	0.28	0.45	**0.82**	**0.71**
GVI	C–NSc	0.44	0.25	–0.01	0.26	0.13	0.50
NGC†	GVI	0.26	0.33	–0.12	0.01	0.27	0.33
NGC†	C–NSc	**0.67**	**0.67**	0.33	0.44	**0.81**	**0.69**

Method		Pearson correlation coefficient					
		Complex				Monomer	Control
		Interface area range (Å²)					
		All	≤800	800< and ≤1500	>1500		
NIP	NSc	**0.95**	**0.79**	**0.85**	**0.91**	**0.88**	**0.96**
NIP	GVI	0.40	0.18	–0.08	0.16	0.07	0.39
NIP	C–NSc	**0.98**	**0.92**	0.91	**0.96**	**0.92**	**0.93**
NIP	NGC†	**0.66**	**0.70**	0.32	0.40	**0.83**	**0.75**
NSc	GVI	0.45	0.29	0.05	0.27	0.16	0.46
NSc	C–NSc	**0.95**	**0.75**	**0.81**	**0.93**	**0.83**	**0.90**
NSc	NGC†	**0.65**	**0.60**	0.28	0.45	**0.82**	**0.71**
GVI	C–NSc	0.44	0.25	–0.01	0.26	0.13	0.50
NGC†	GVI	0.26	0.33	–0.12	0.01	0.27	0.33
NGC†	C–NSc	**0.67**	**0.67**	0.33	0.44	**0.81**	**0.69**

GVI: Gap Volume Index (*Laskowski, 1995*)

NGC: Normalized Grid Correlation (*Katchalski-katzir et al, 1992*)

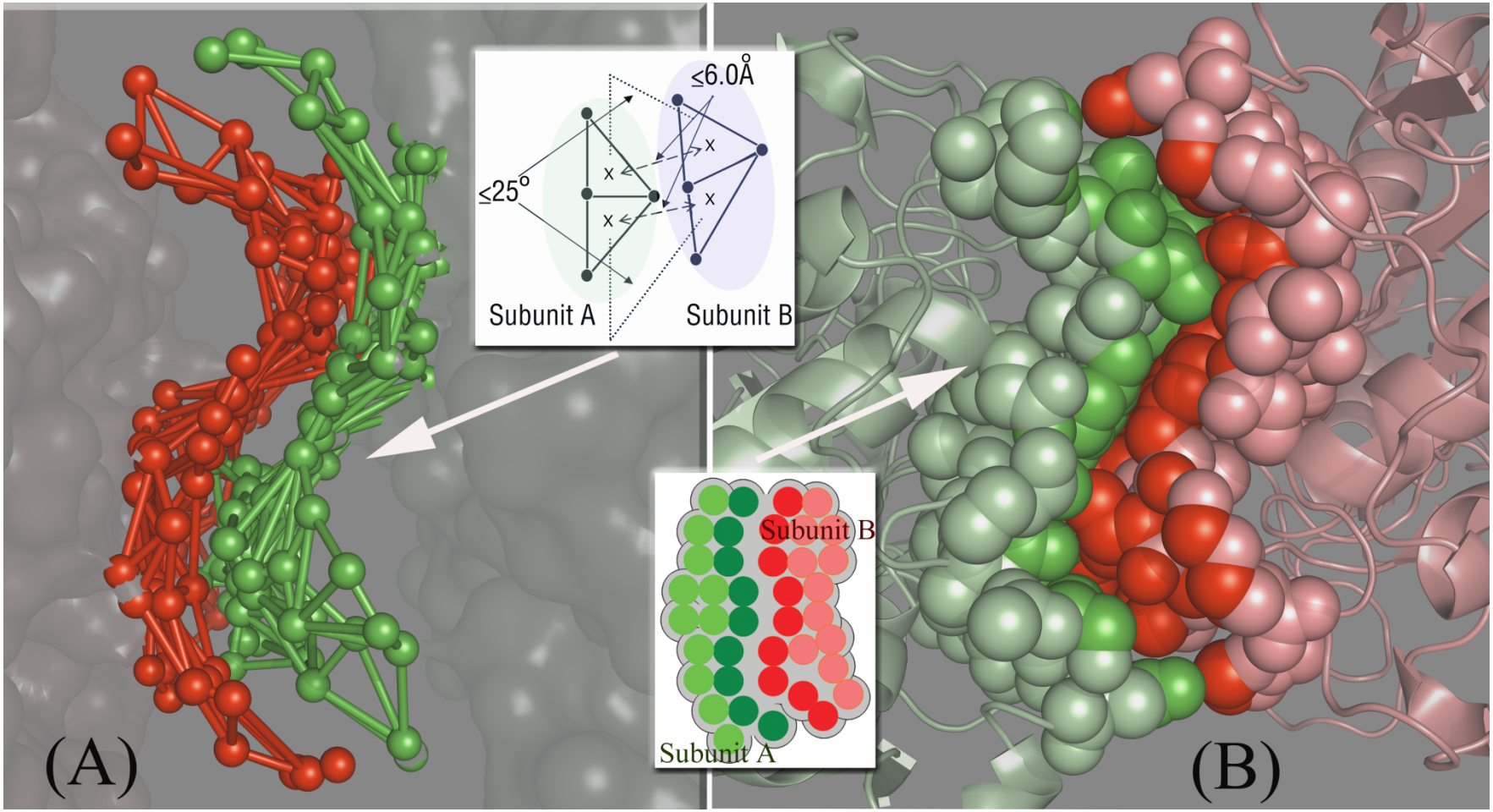
C-NSc: CCP4 Normalized Surface Complementarity (*Lawrence & Colman, 1993*)

#binary complexes = 906

#monomers = 386

control set = 100

Designing New Measures for surface complementarity and

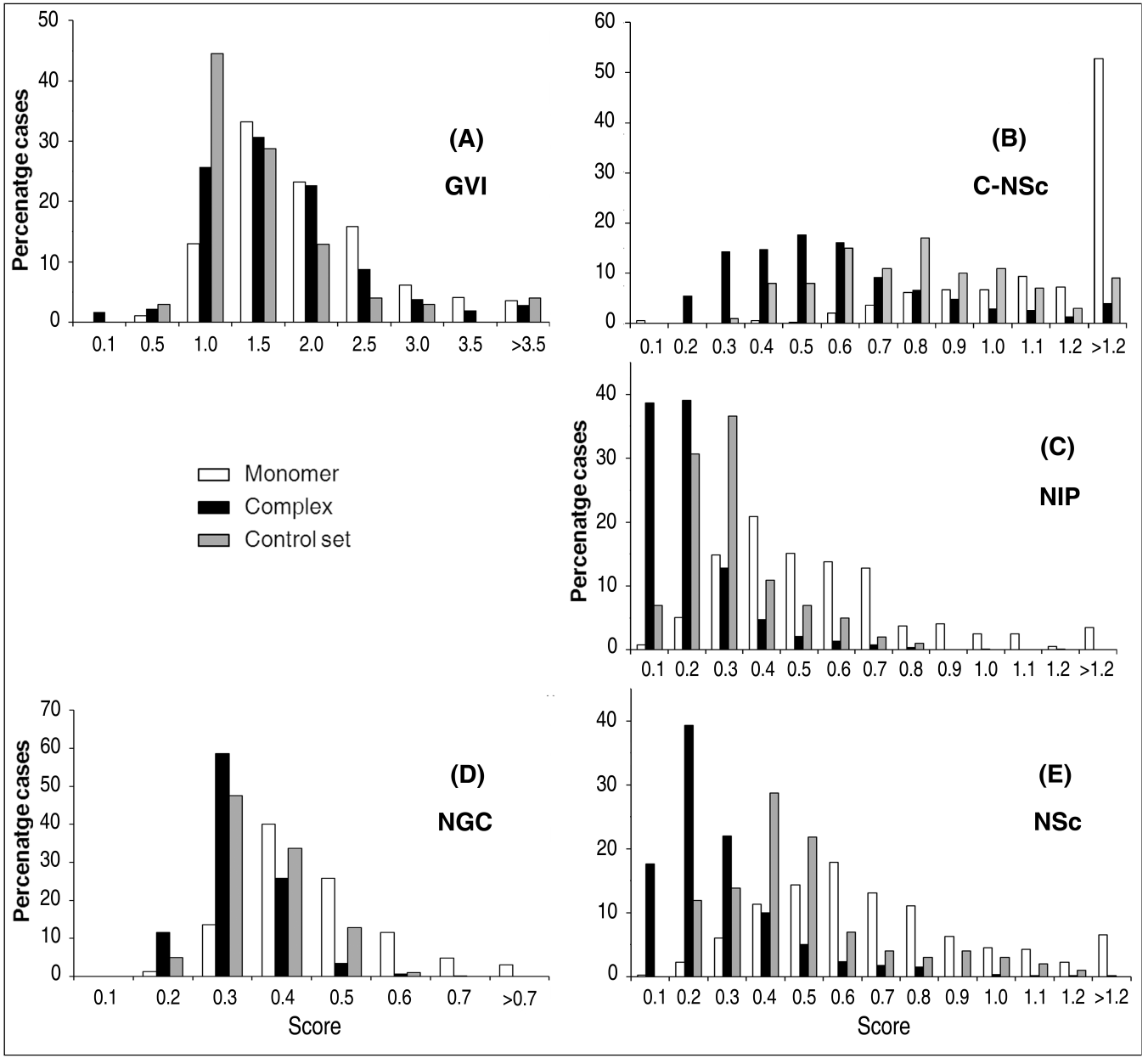


2/4/11

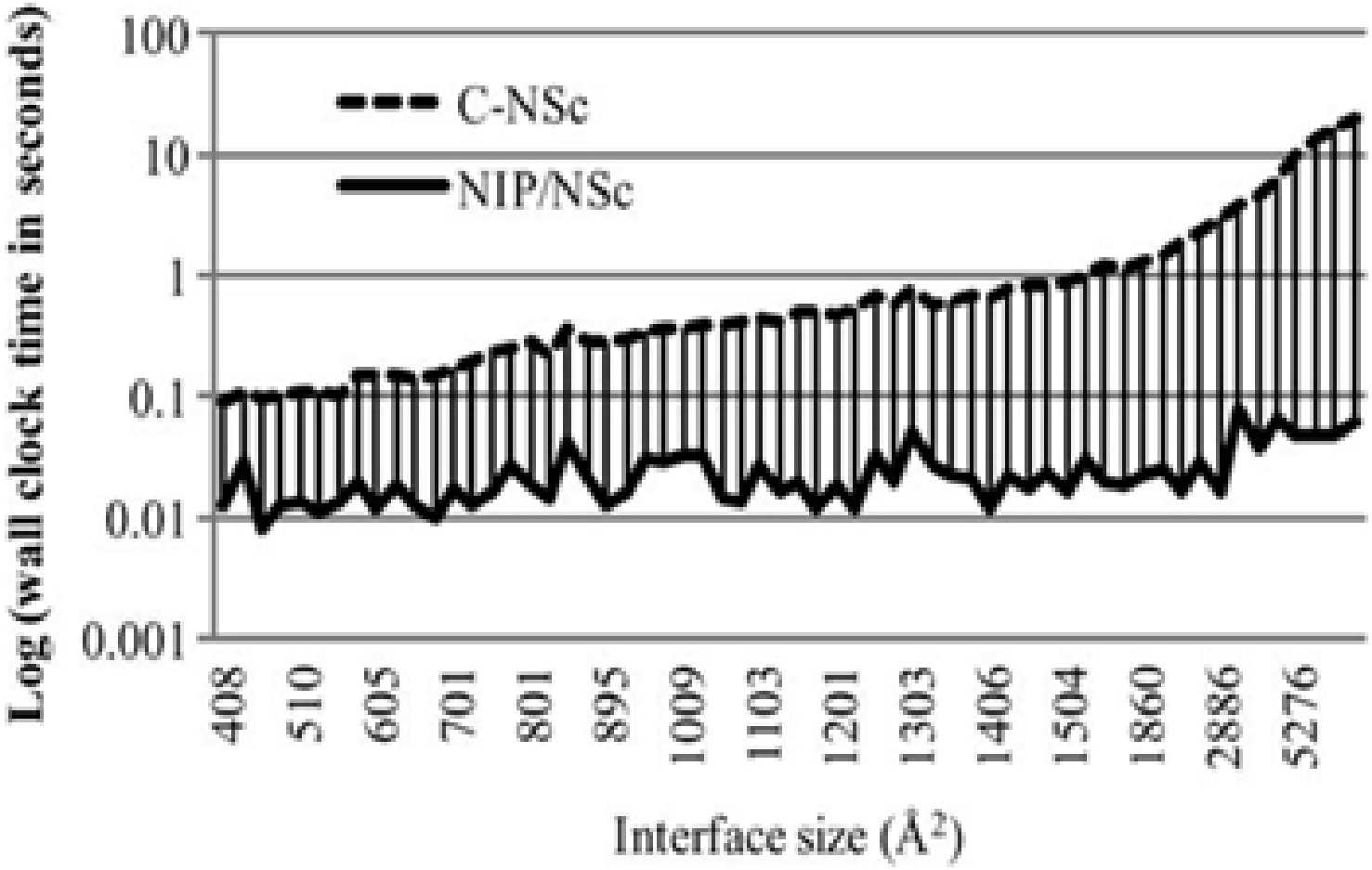
New efficient measures of surface complementarity and interface packing

Method		Pearson correlation coefficient					
		Complex				Monomer	Control
		Interface area range (Å^2)					
		All	≤800	800< and ≤1500	>1500		
NIP	NSc	**0.95**	**0.79**	**0.85**	**0.91**	**0.88**	**0.96**
NIP	GVI	0.40	0.18	-0.08	0.16	0.07	0.39
NIP	C-NSc	**0.98**	**0.92**	0.91	**0.96**	**0.92**	**0.93**
NIP	NGC†	**0.66**	**0.70**	0.32	0.40	**0.83**	**0.75**
NSc	GVI	0.45	0.29	0.05	0.27	0.16	0.46
NSc	C-NSc	**0.95**	**0.75**	**0.81**	**0.93**	**0.83**	**0.90**
NSc	NGC†	**0.65**	**0.60**	0.28	0.45	**0.82**	**0.71**
GVI	C-NSc	0.44	0.25	-0.01	0.26	0.13	0.50
NGC†	GVI	0.26	0.33	-0.12	0.01	0.27	0.33
NGC†	C-NSc	**0.67**	**0.67**	0.33	0.44	**0.81**	**0.69**

NIP: Normalized interface packing
NSc: Normalized surface complementarity


Percenatge cases
(A)
GVI
(B)
C-NSc
(C)
NIP
(D)
NGC
(E)
NSc
Monomer
Complex
Control set
Score
Score

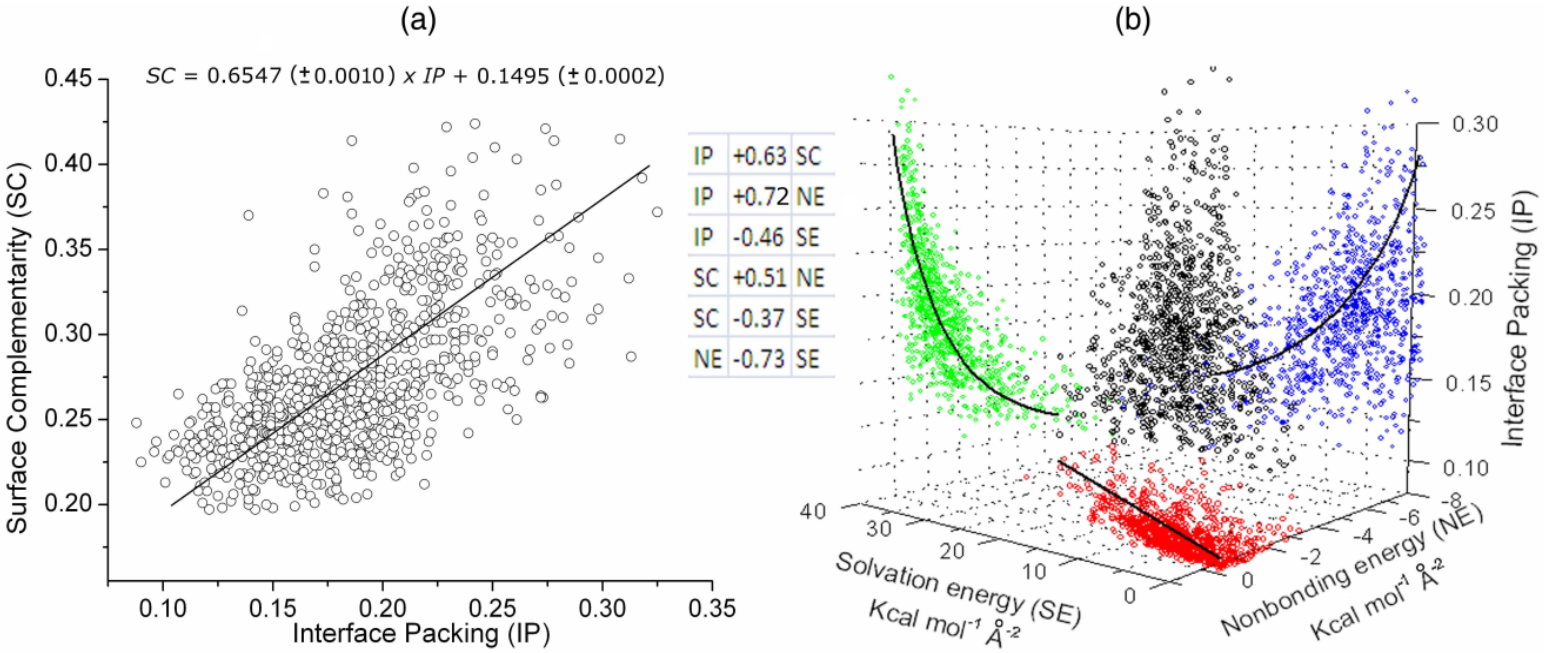
Discrimina



Time efficient

http://pallab.serc.iisc.ernet.in/probe

Mitra & Pal, J. Comp. Chem (2010)



- Interface area (IA)
- Normalized interface packing (NIP)
- Normalized surface complementarity (NSc)

- Non-bonded energy (NE):

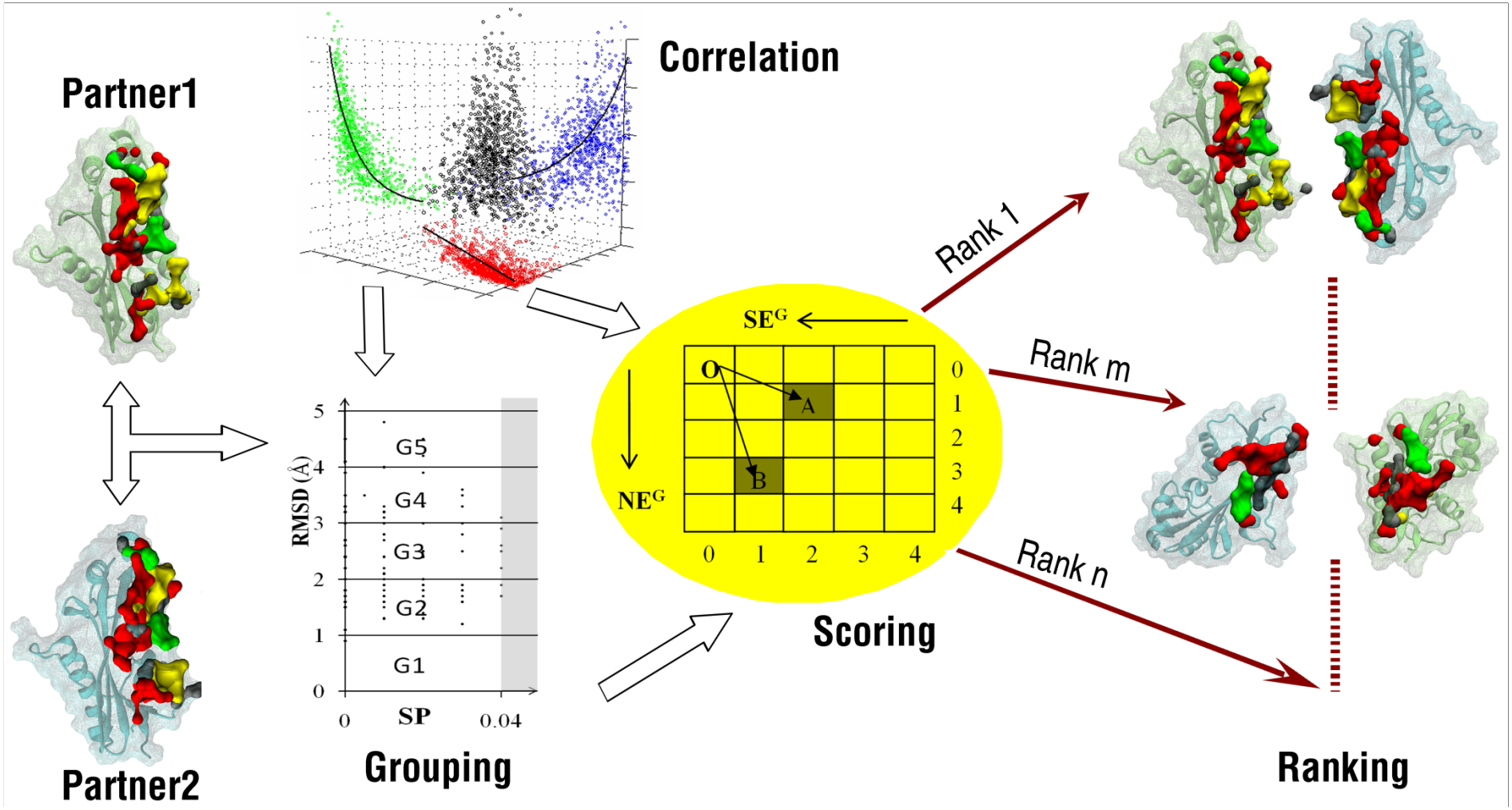
$$NE = \sum_{i<i}^{atoms} \left(\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{4\Pi\varepsilon R_{ij}} \right)$$

- Solvation energy (SE):

$$SE = \sum_{\text{interface atoms}} \Delta\sigma(\text{Atom Type}) \times \Delta\text{ASA}$$

2/4/11

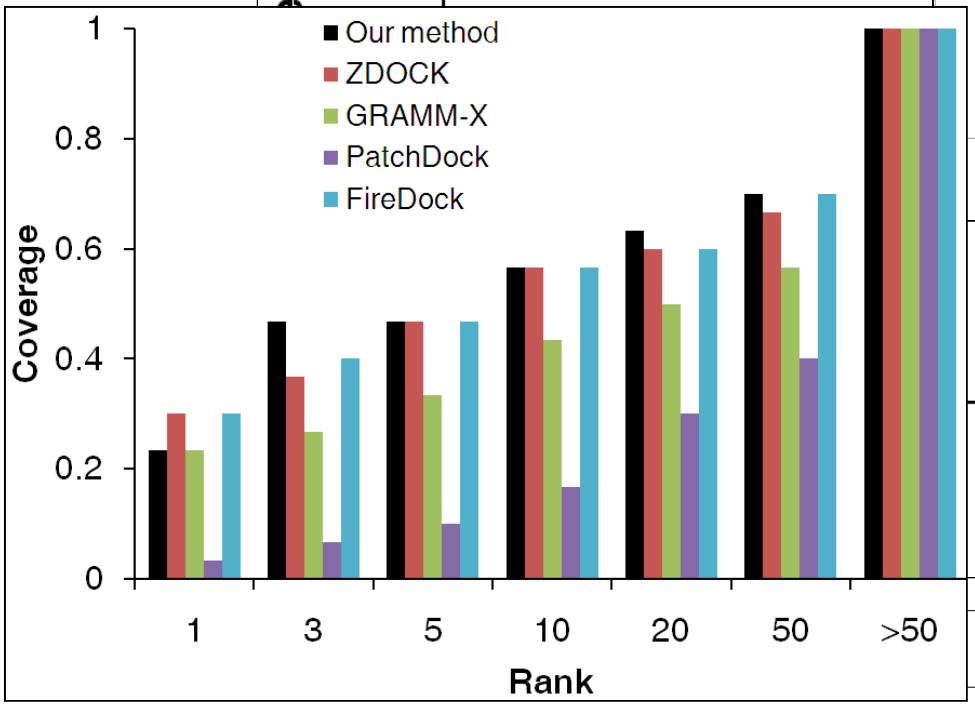
Method design

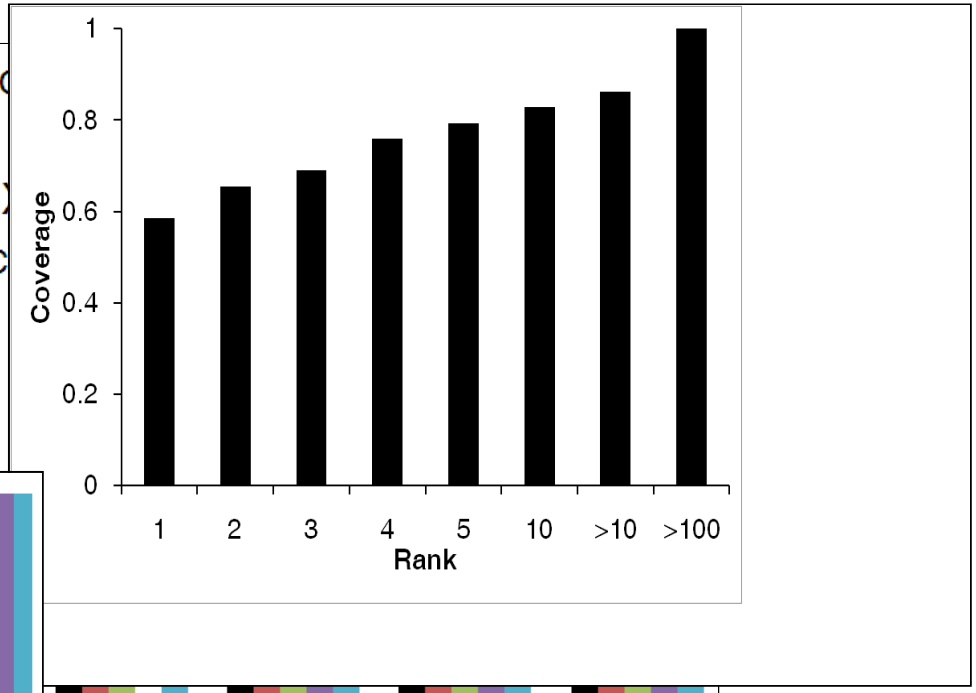


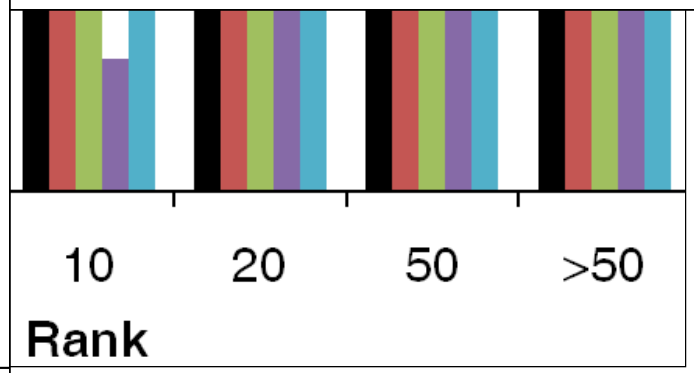
http://pallab.serc.iisc.ernet.in/probe

Efficient docking using simple approach

Predictive Docking – ranking decoys







Bibliography

- Using correlated parameters for improved ranking of protein-protein docking decoys. Pralay Mitra and Debnath Pal. Journal of Computational Chemistry (2010)
- New measures for estimating surface complementarity and packing at protein-protein interfaces. Pralay Mitra and Debnath Pal. FEBS Letters **584**, 1163-1168 (2010)

Acknowledgment

- Department of Biotechnology

Thank You