

MCSS with hybrid solvent models

qualitative docking & screening powers of nucleotidic
ligands

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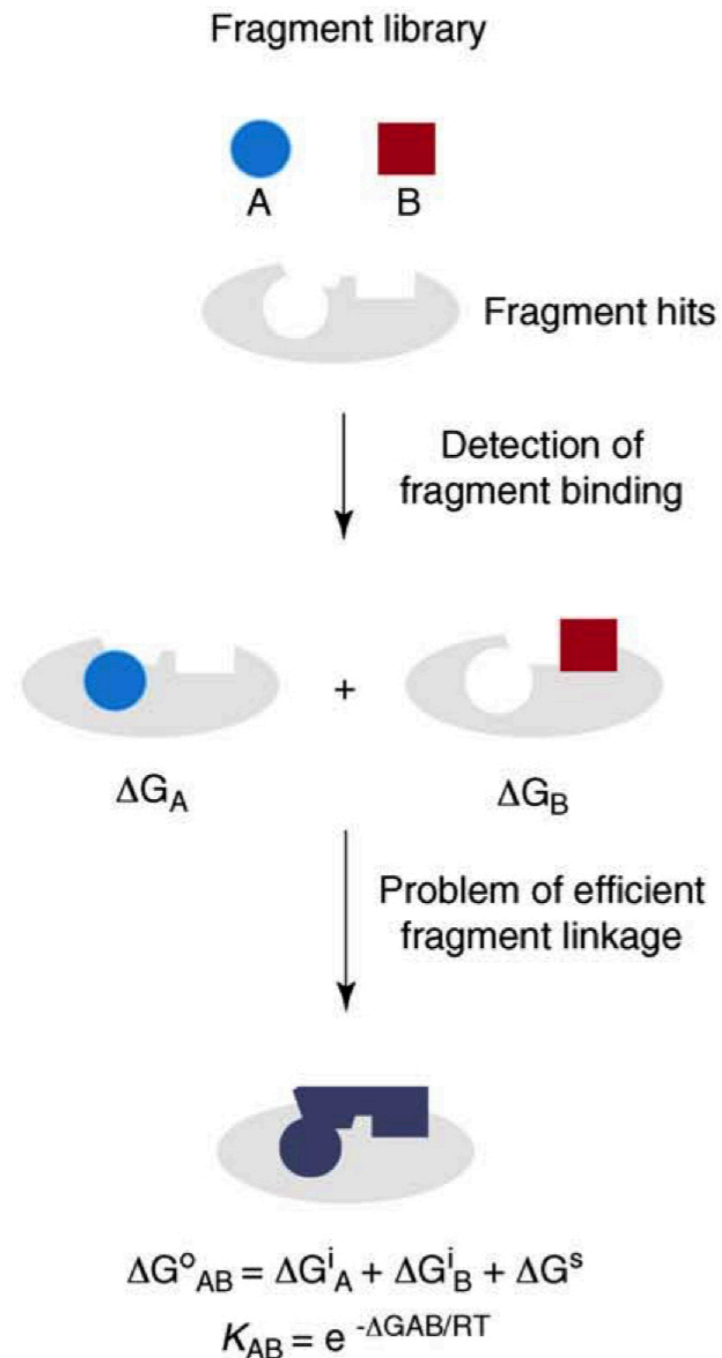
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Fragment-based design/ discovery (FBD) approaches

in silico



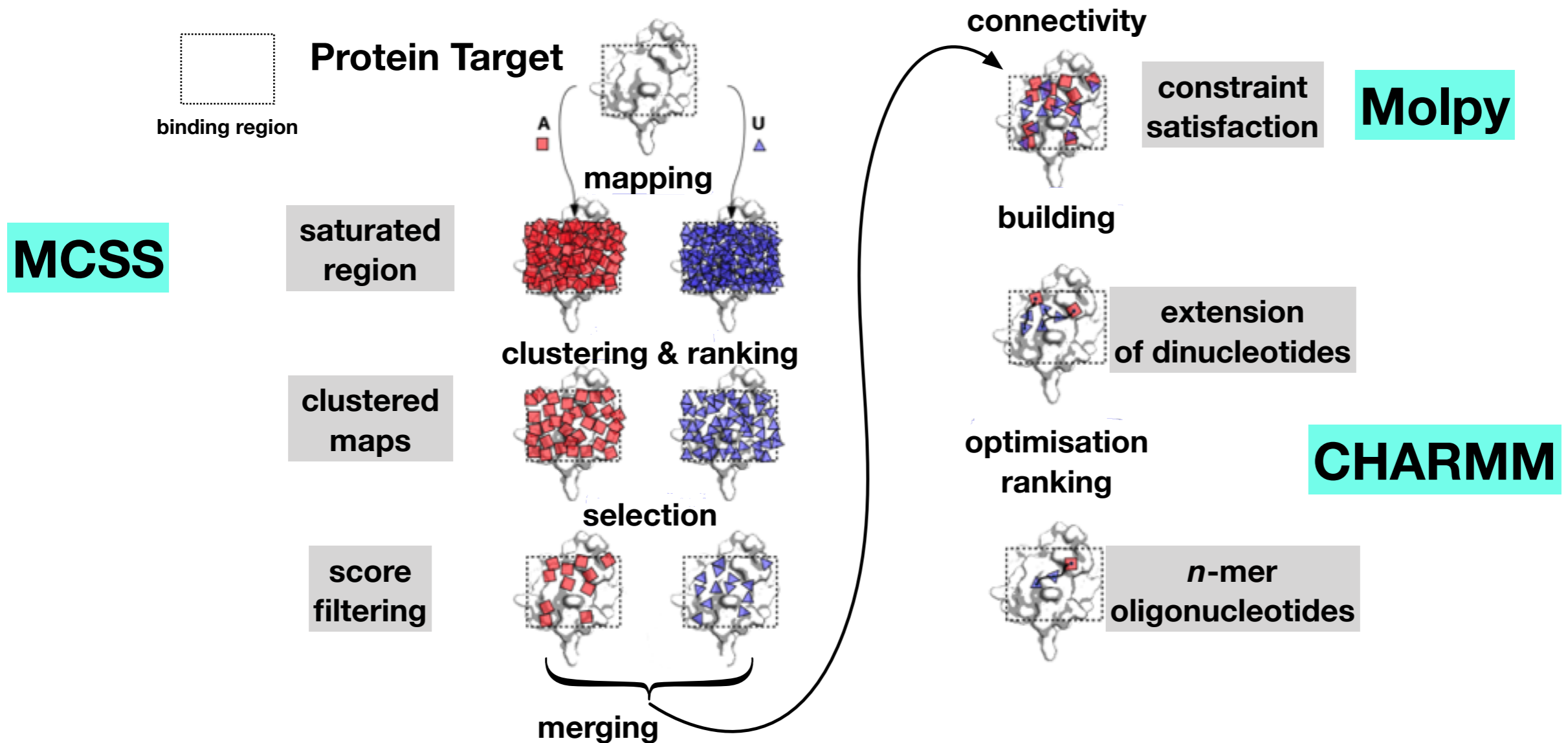
**high-resolution structure
(biologically relevant conformations)**

more fitted fragments

docking power (native)

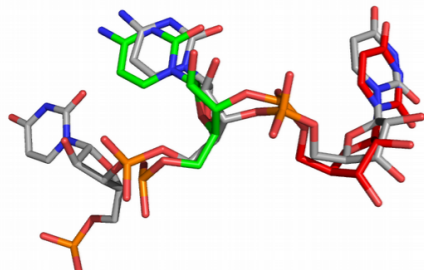
screening power (true binders)

MCSS-based workflow for FBD of oligonucleotides

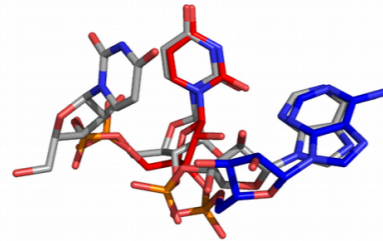


Preliminary results on RBPs

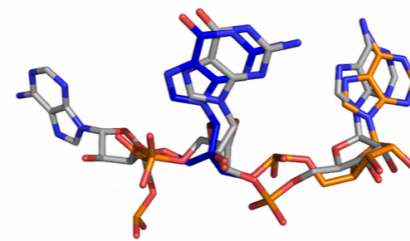
MCSS+Molpy+CHARMM



2XNR
(RRM)



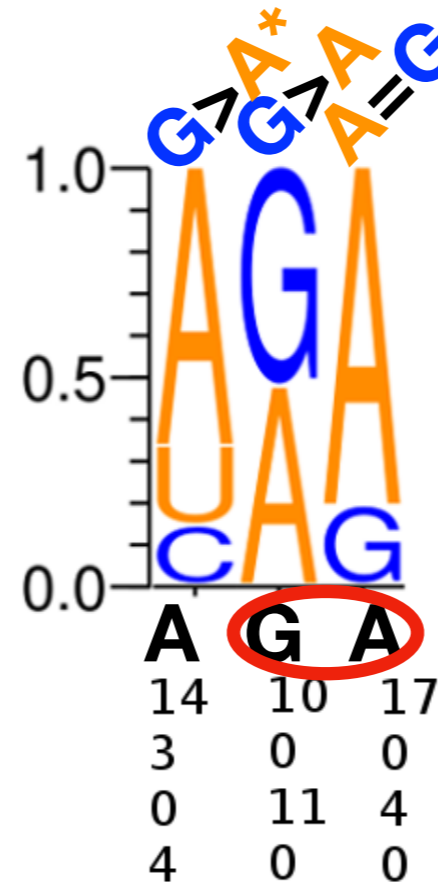
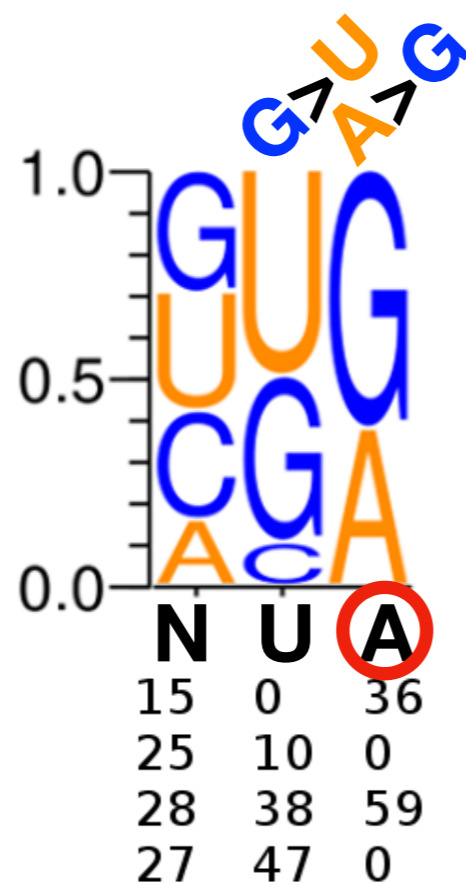
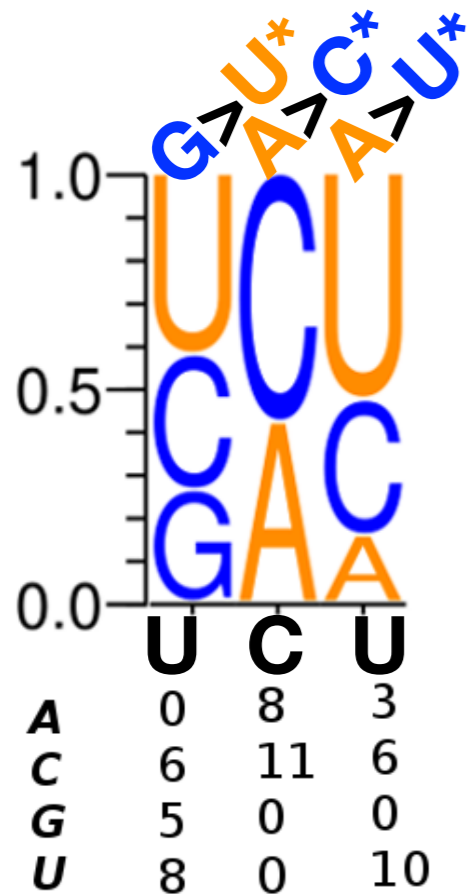
5ELH
(KH)



5WWX
(CCCH)

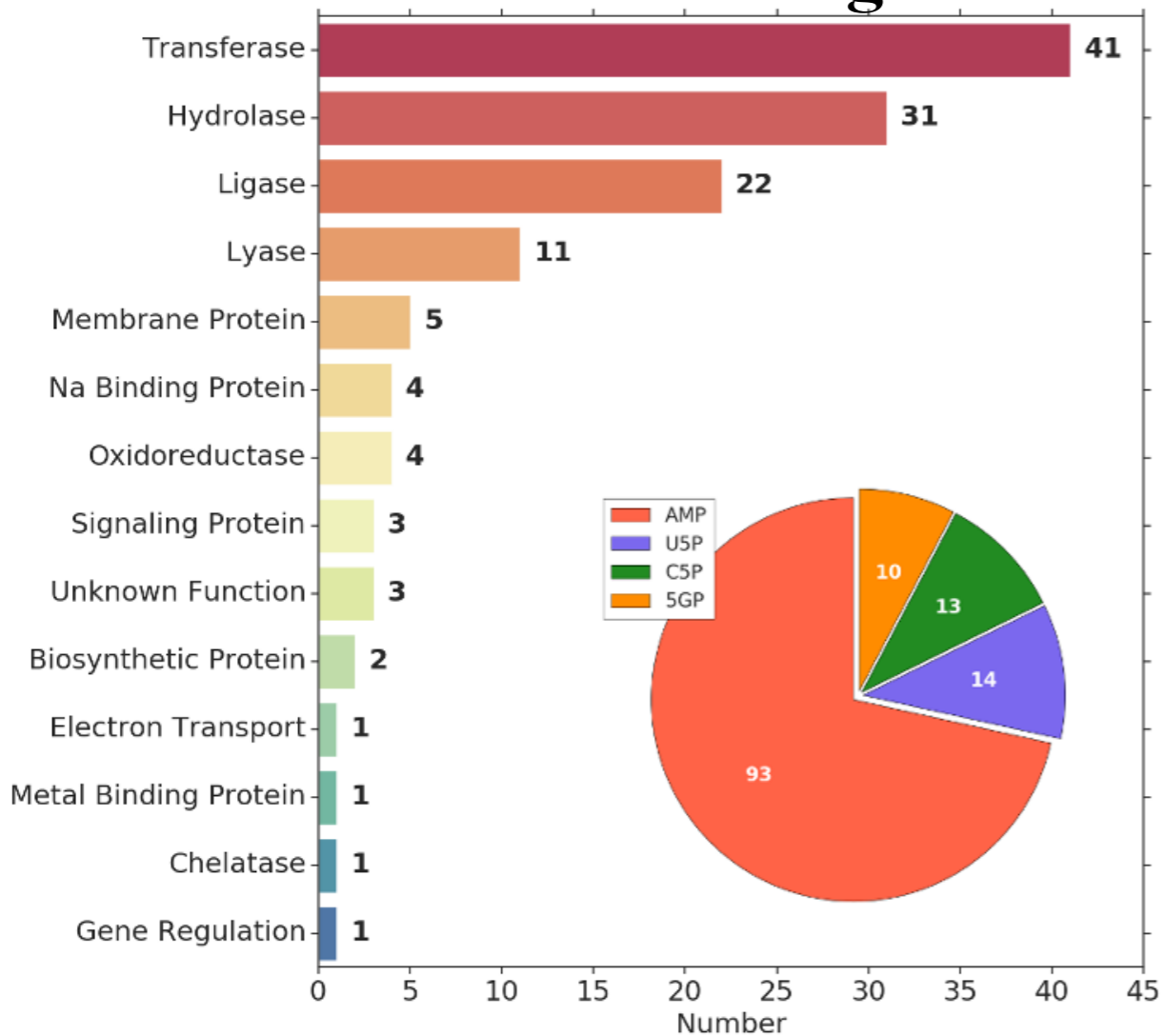
+ sequence constraint
 $\text{RMSD} \leq 1.5\text{\AA}$
 Top-1

- sequence constraint
 score-based nucleotide
 preferences



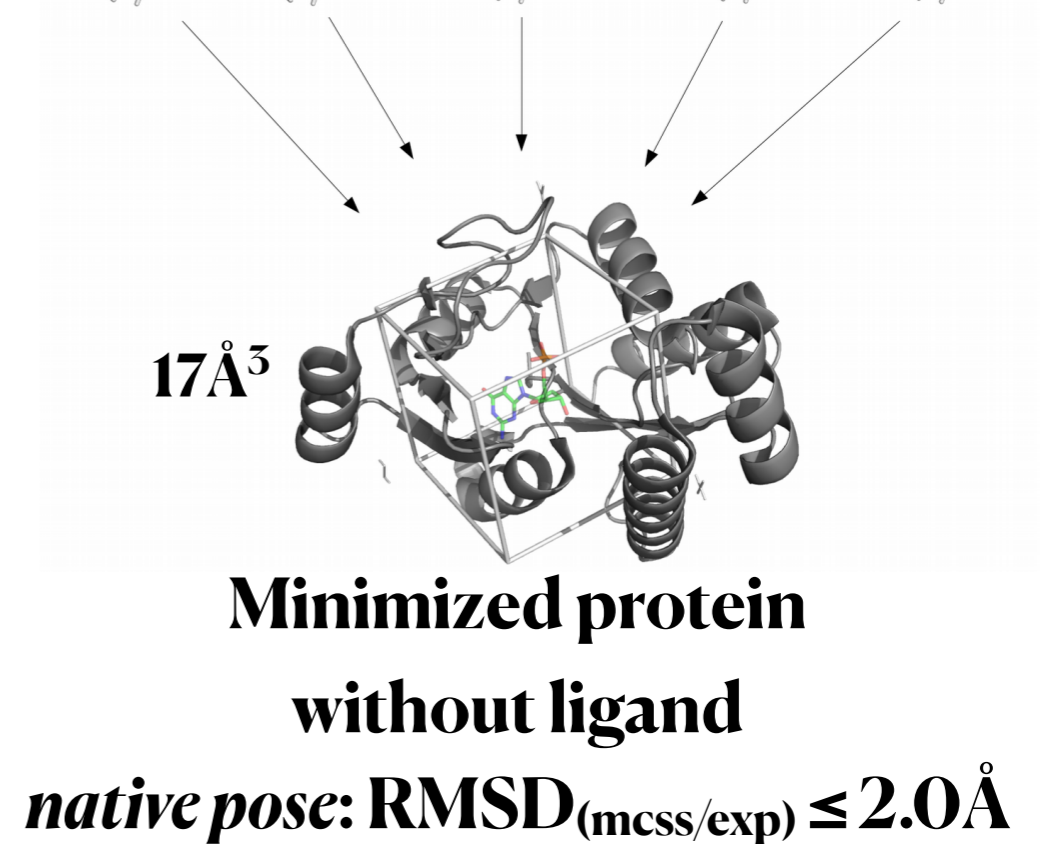
Nucleotide-Protein Complexes (benchmark120)

Nucleotide Binding Sites

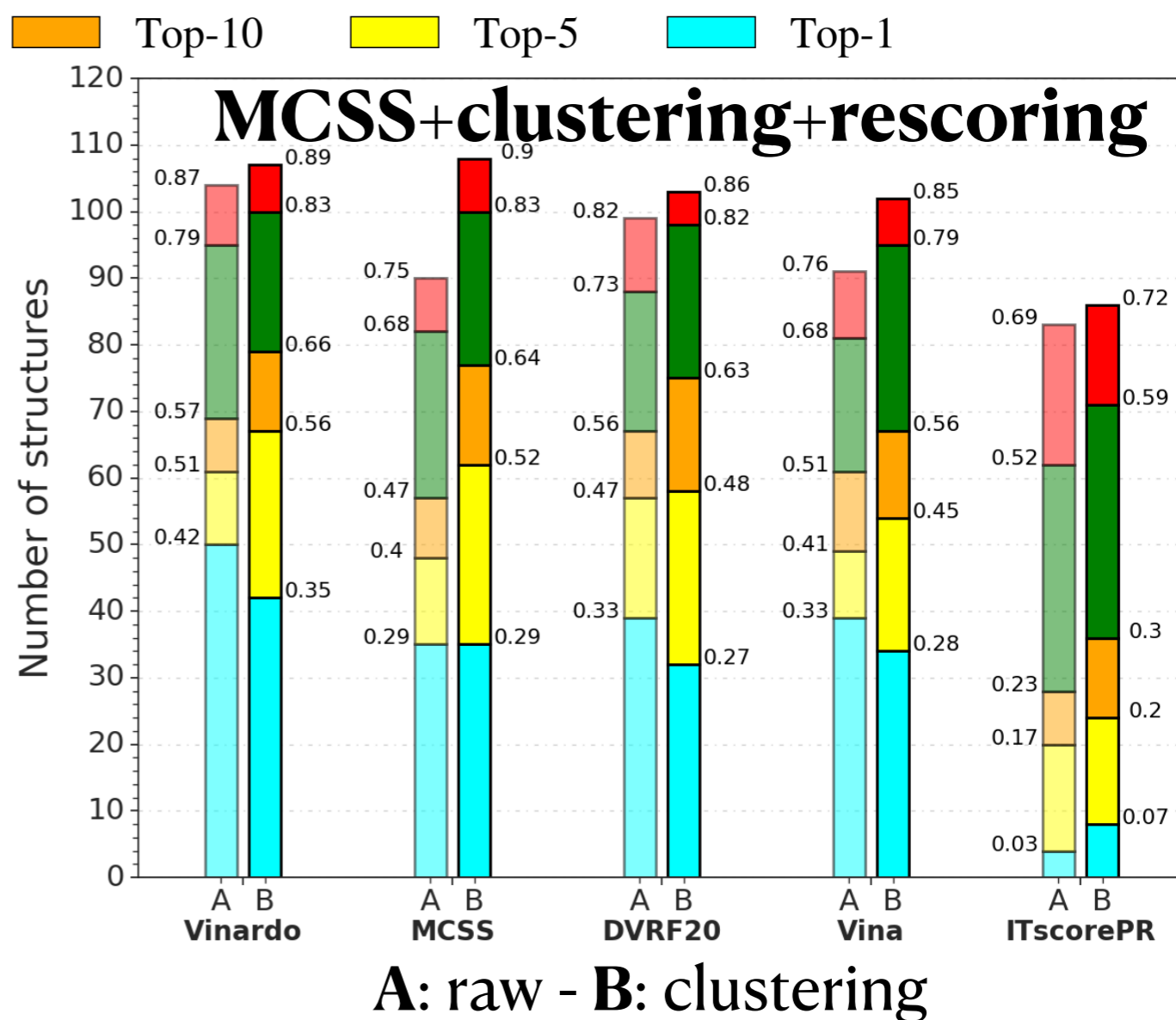
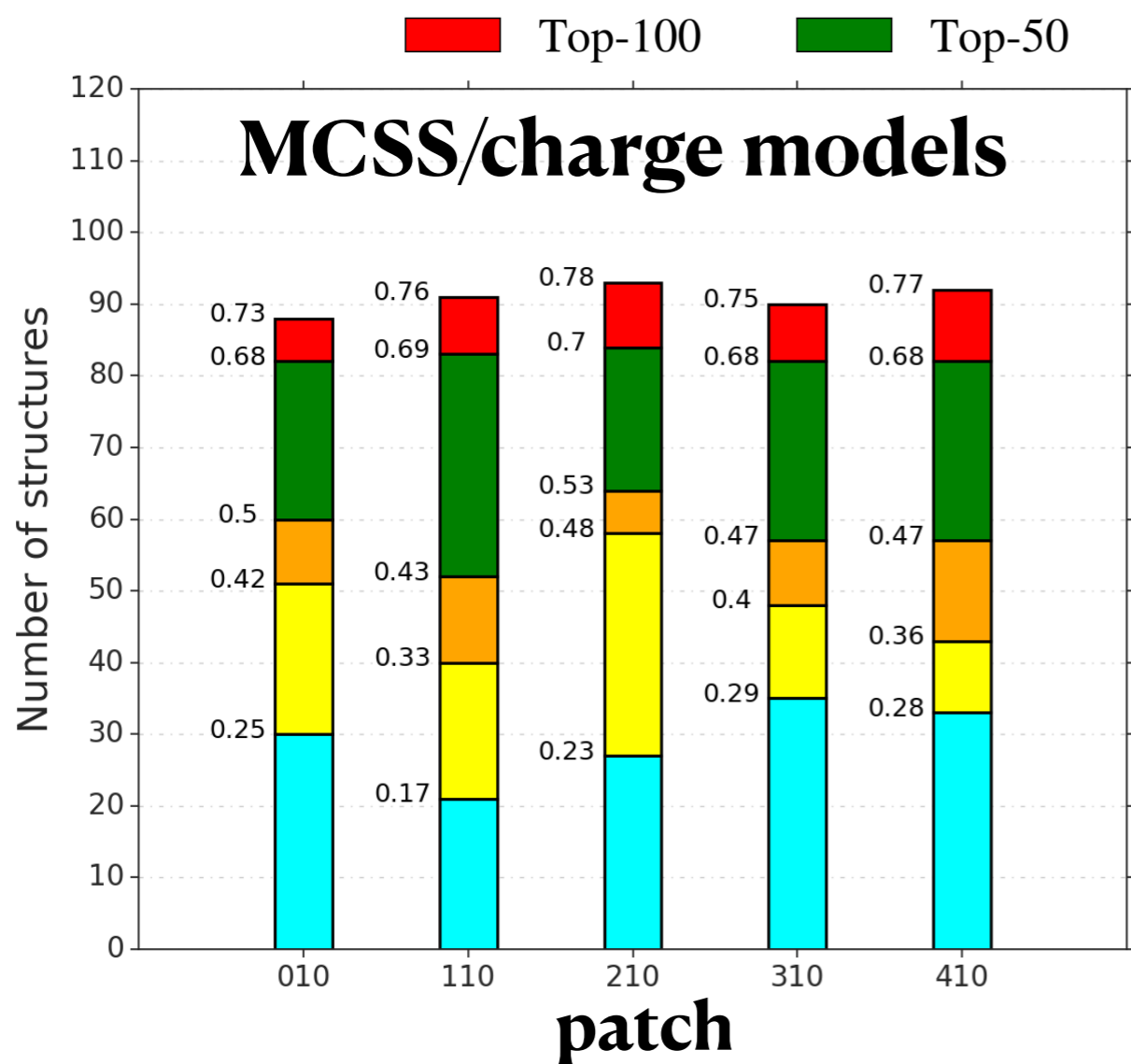


high resolution, non-redundant, etc

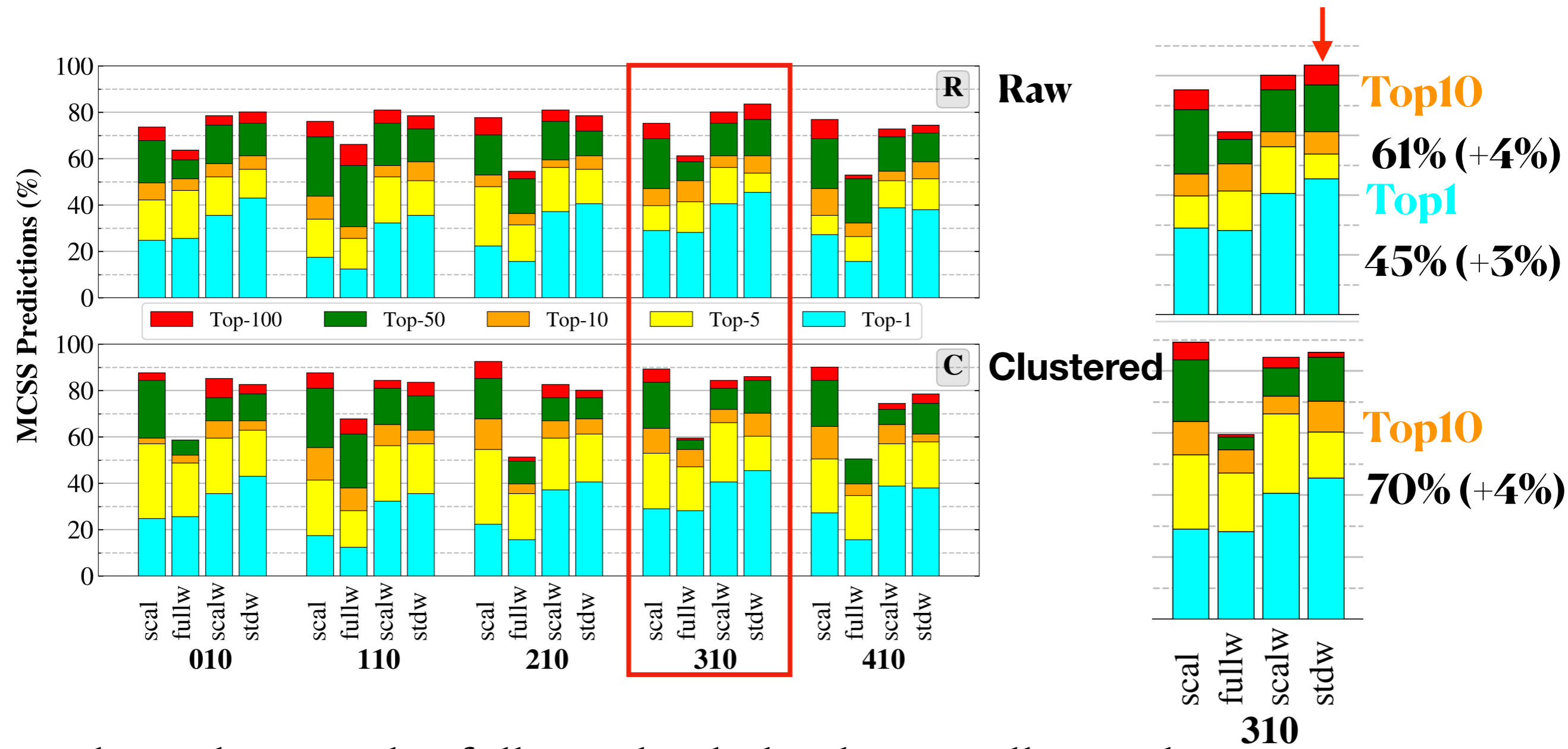
5' patches R010 R110 R210 R310 R410
 R=A,C,G,U



Docking Power: MCSS/Empirical Scoring



Docking Power: Implicit/Hybrid Solvent Models

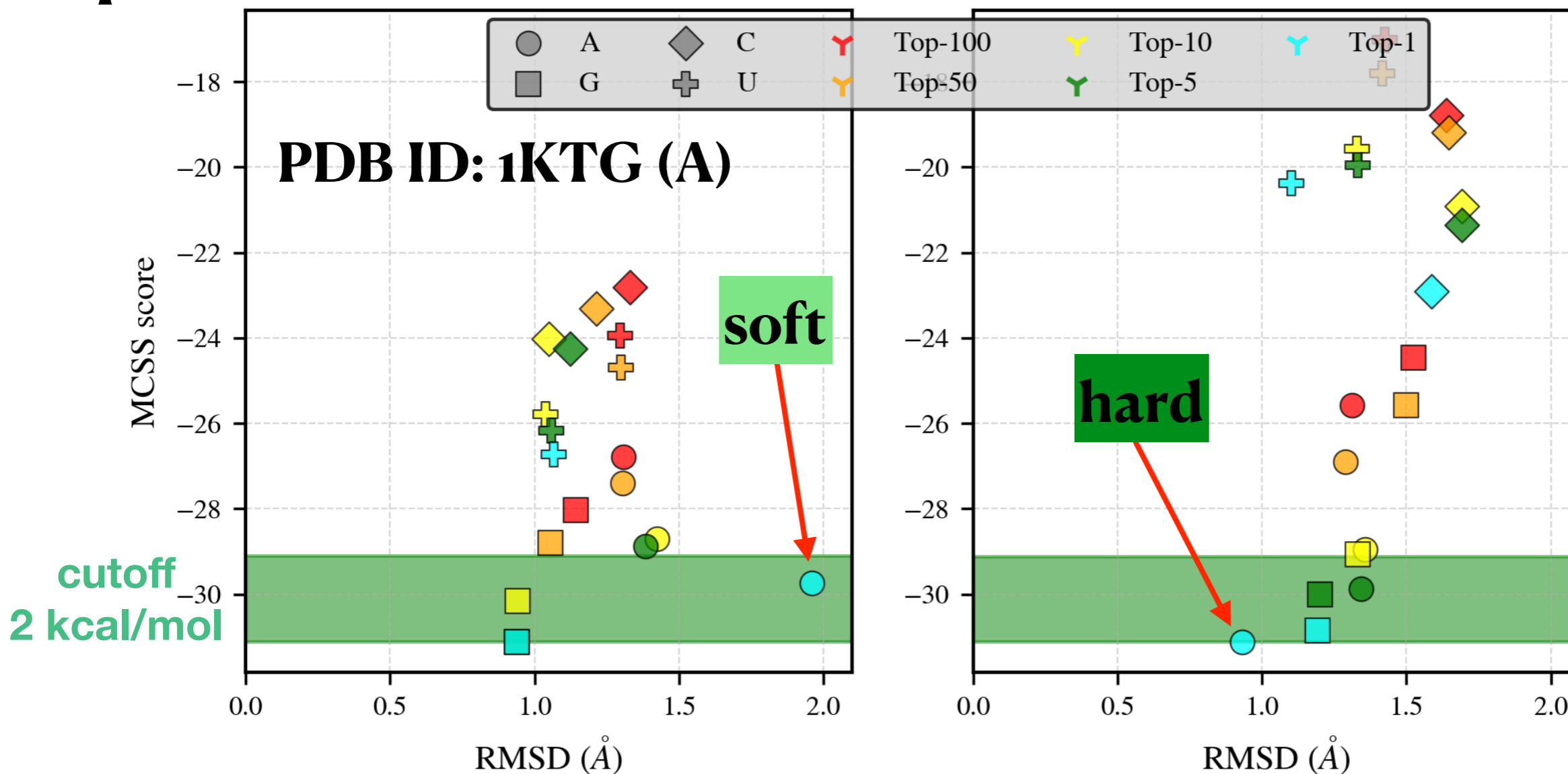


scal=implicit; scalw, fullw, stdw=hybrid (crystallographic waters - TIP3P)

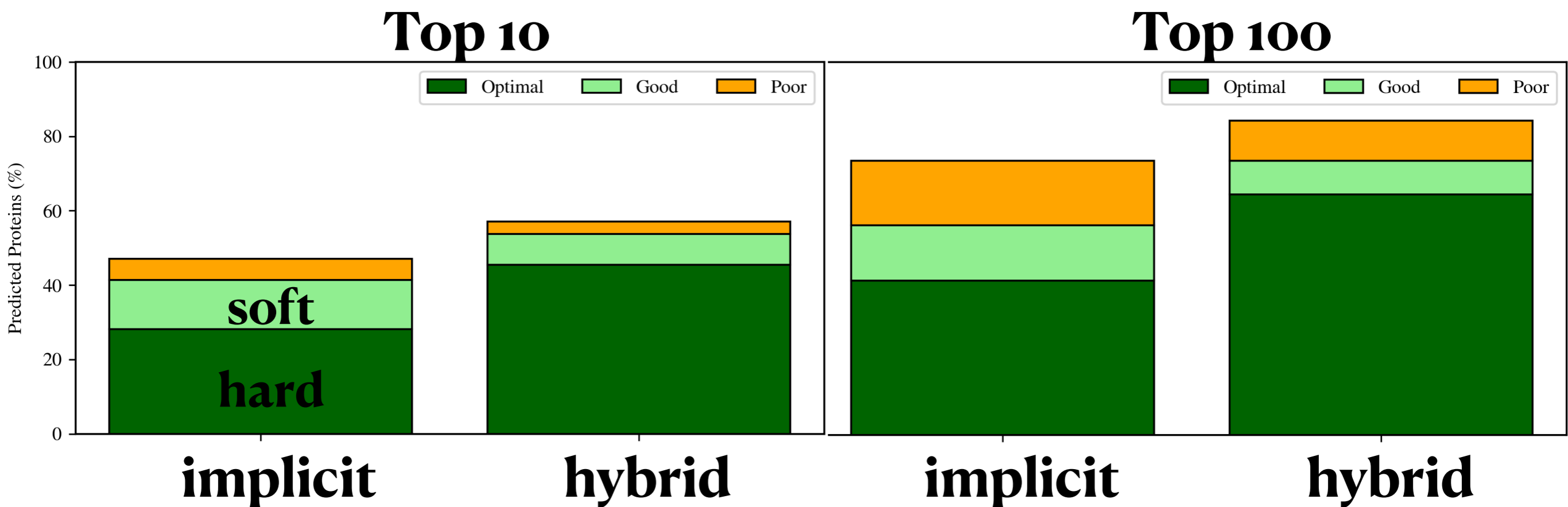
Screening Power: Hard/Soft Predictions

implicit

hybrid



Screening Power: Implicit/Hybrid Solvent Models



Conclusions

- **fragment-based** approach applied to single nucleotide binding
- **explicit solvent** improve predictions of nucleotide binding
 - improved docking power (native poses)
 - improved screening power (“true” binders)
- other solvent implementations to evaluate ...

Acknowledgments

- MCSS:
 - Roy González-Alemán (Ph.D. student, 2019-)
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 - Martin Karplus
 - Qiang Cui

