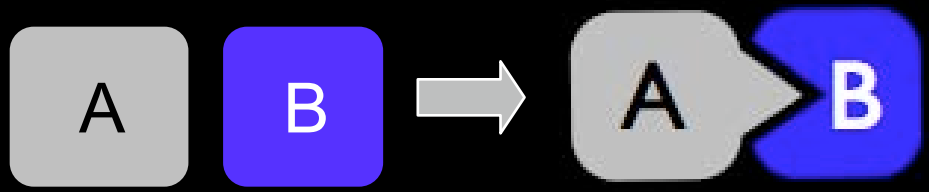
Protein Interface Design

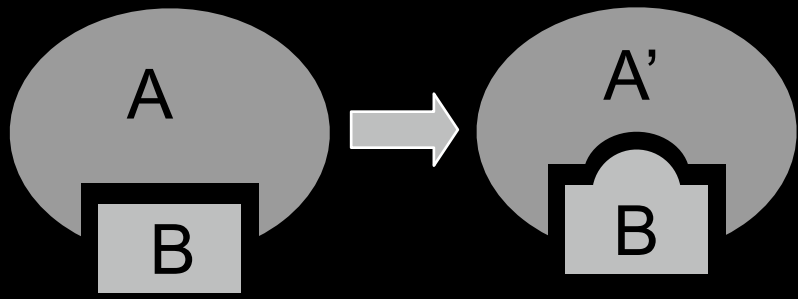
Tanja Kortemme
UCSF

Protein Interface Design - Concepts

Optimize Interaction

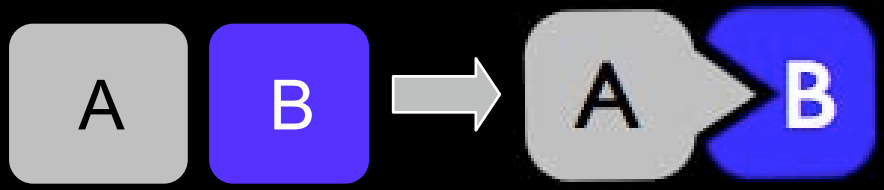


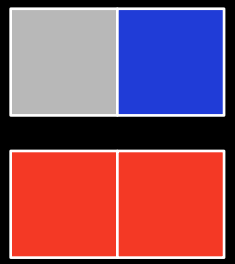
Altered Specificity



Protein Interface Design

- optimize an interaction

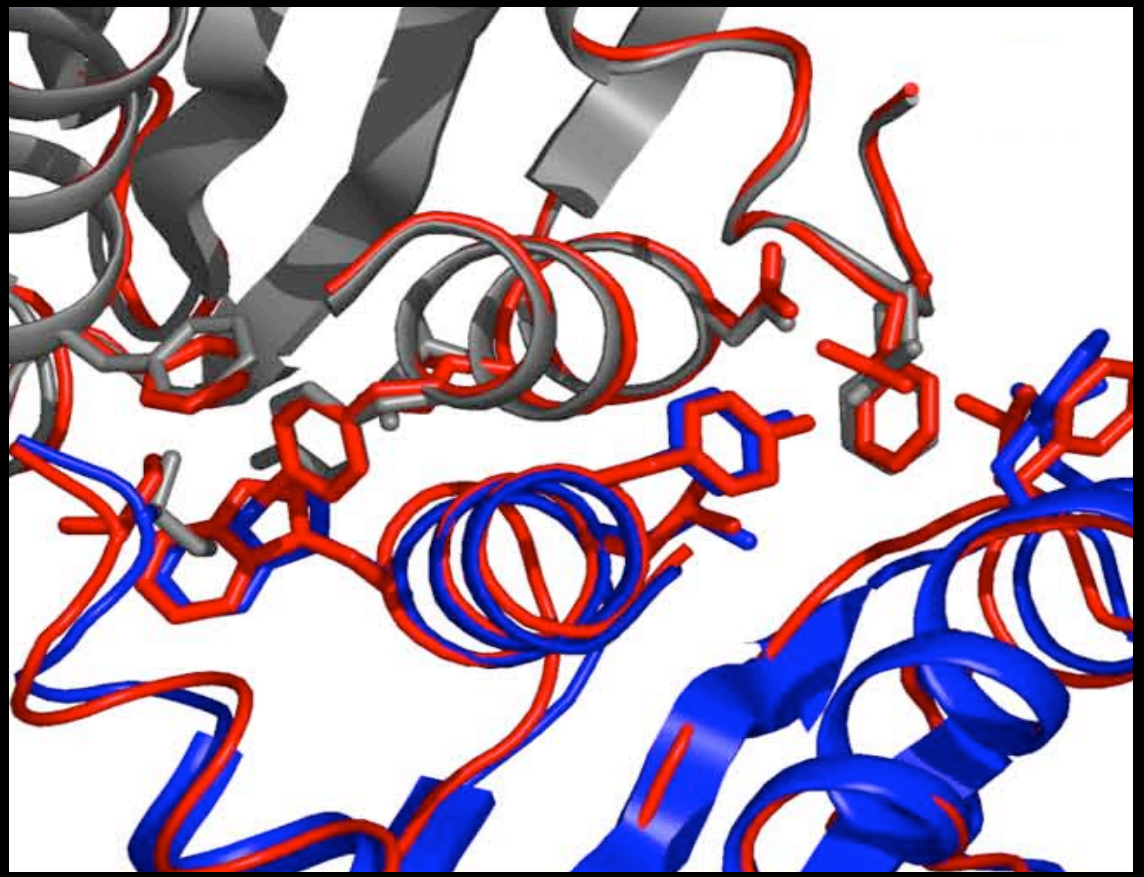




X-ray

DESIGN

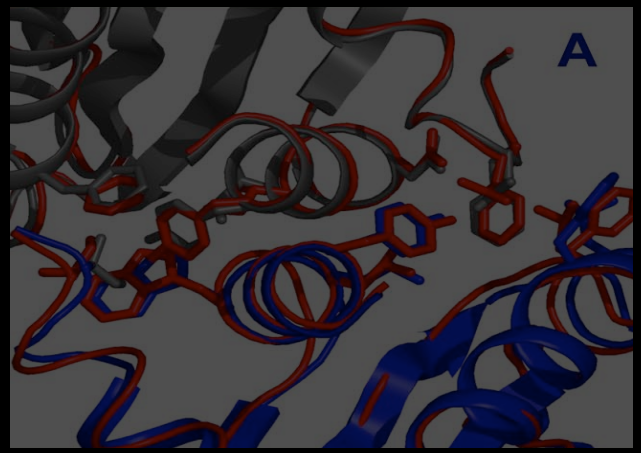
$8x10^{17}$ possible sequences
$6x10^{37}$ possible structures



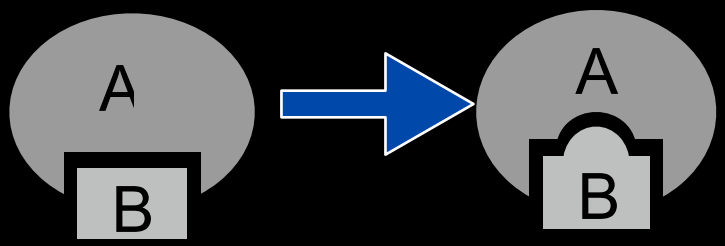
Mol Cell 2002
with Brett Chevalier & Barry Stoddard

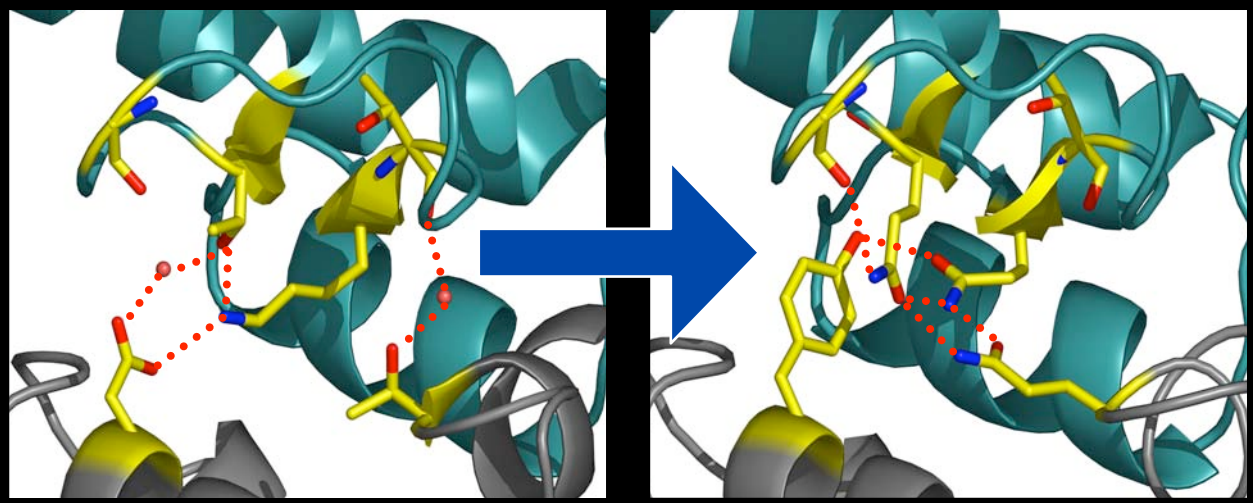
Protein Interface Design

- optimize an interaction



- alter specificity:
  remodel a hydrogen bonding network

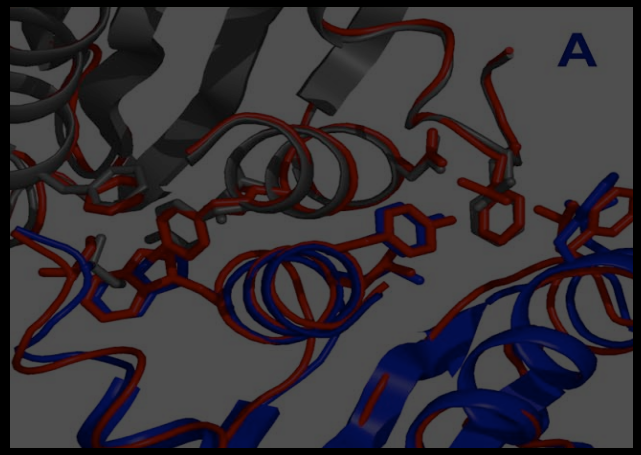




with Lukasz Joachimiak
J. Mol. Biol. 2006

Protein Interface Design

- optimize an interaction



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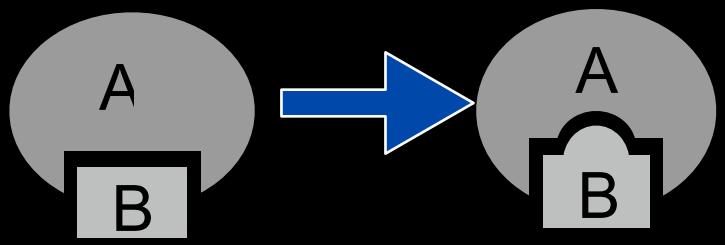
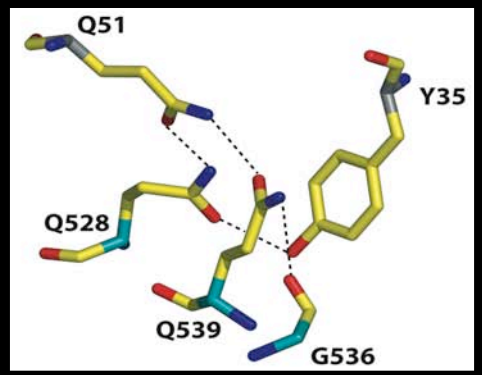
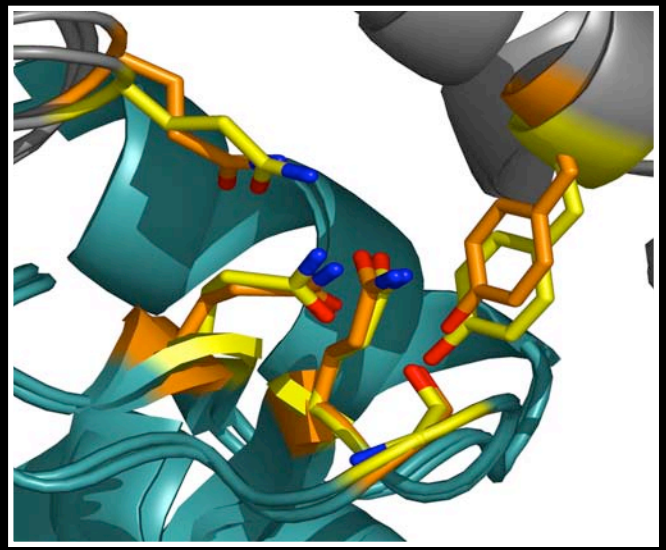


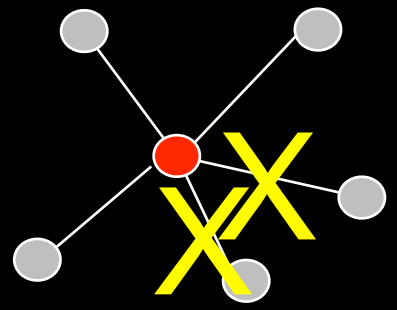




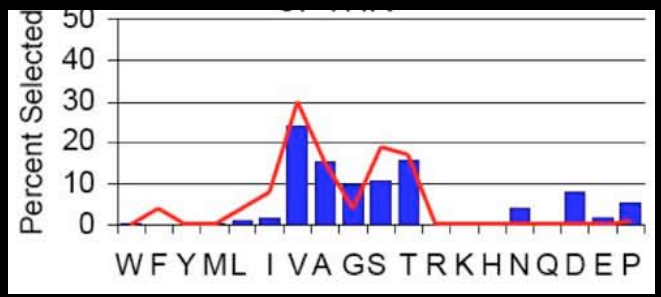
with Lukasz Joachimiak
J. Mol. Biol. 2006

OUTLINE

- reengineer protein interaction specificity



- flexible backbone design to predict tolerated sequences & libraries



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OUTLINE

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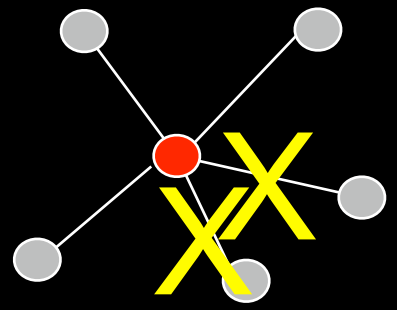

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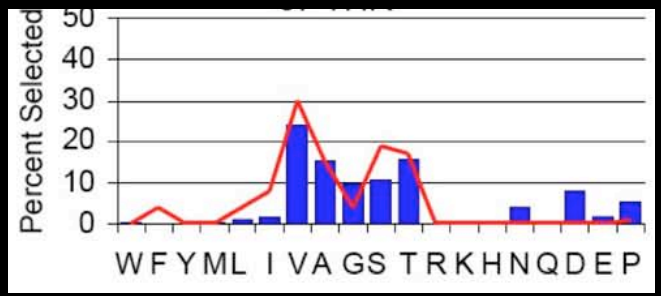

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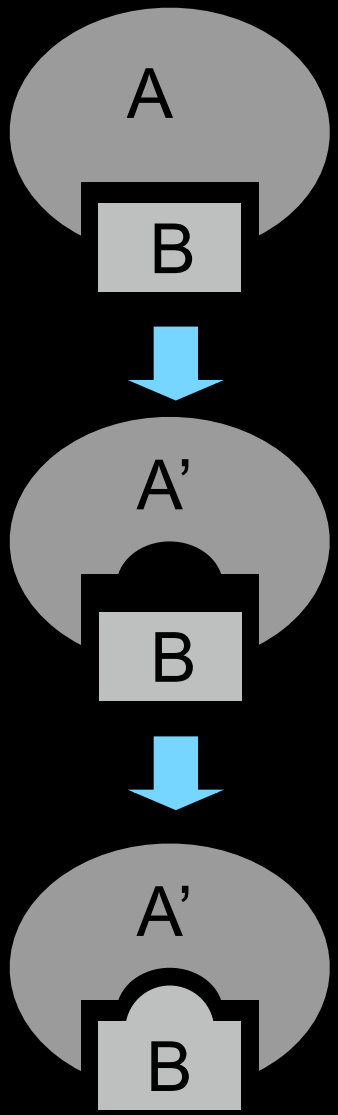
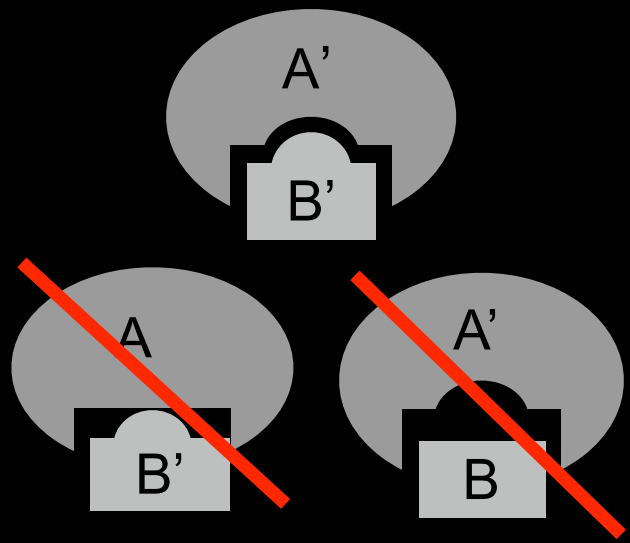
Computational Second Site Suppressor strategy to REDESIGN PROTEIN INTERACTION



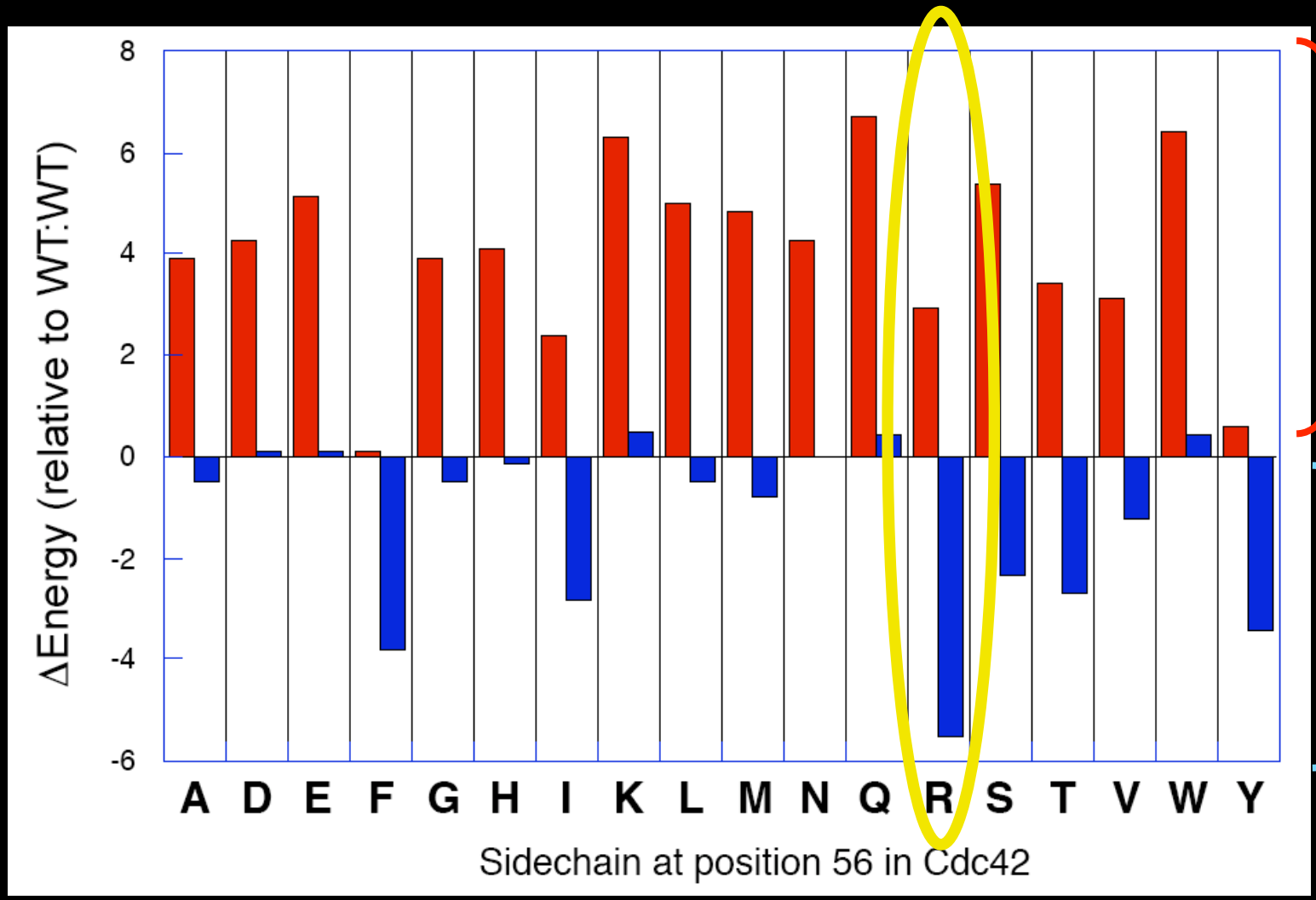
- computationally screen for destabilizing mutations in partner A
- redesign interface on partner B to compensate

select for:

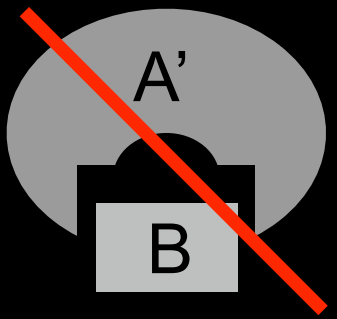


Kortemme, Joachimiak et al. Nature Struct. Mol. Biol. 2004

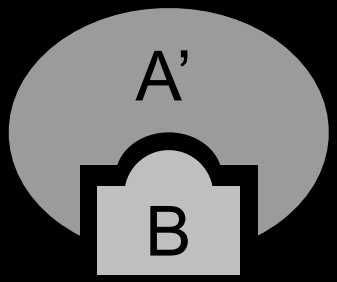
Computational Second Site Suppressor Strategy



predicted destabilization

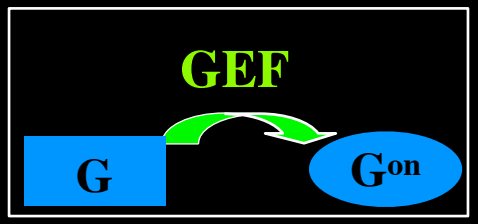


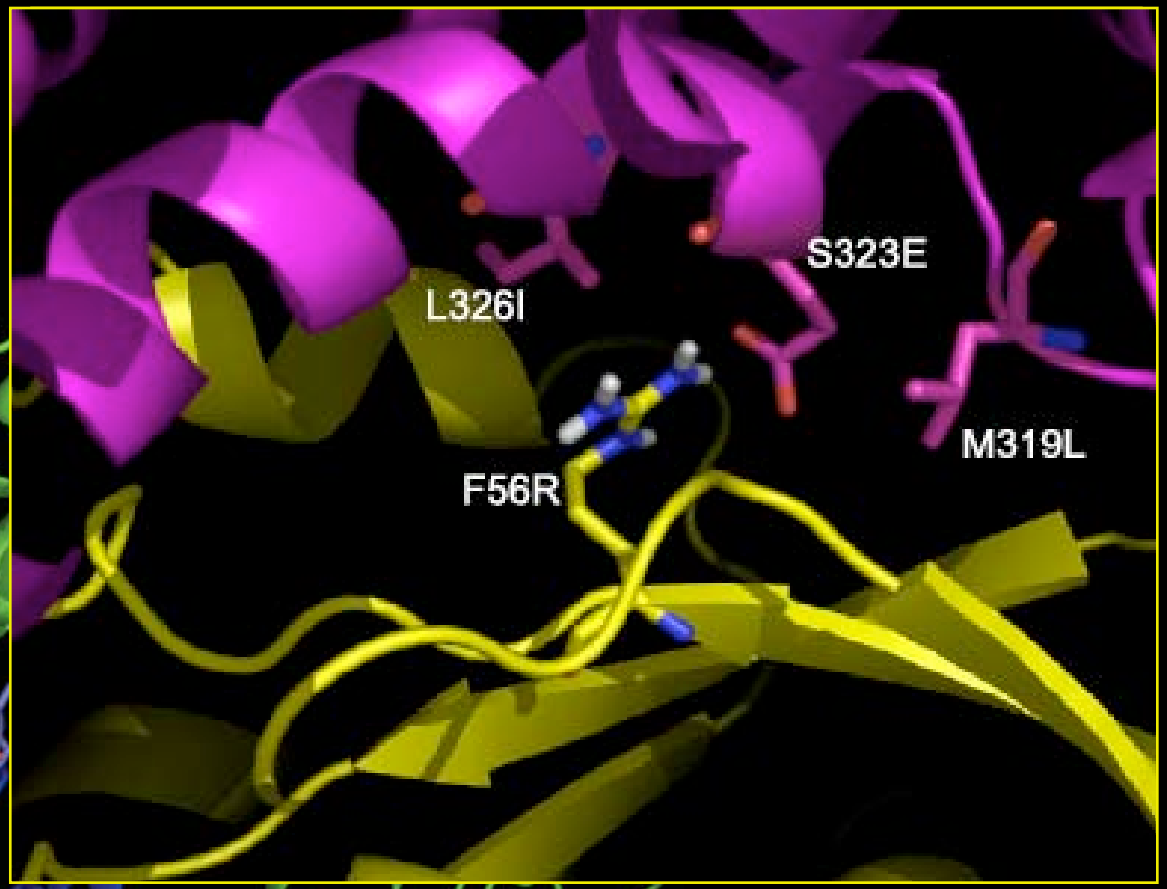
predicted compensation



Greg Kapp

Design of new GTPase/GEF pairs





(predicted)

Cdc42

1KI1.pdb
Snyder et al. (2002) NSB v9 p468

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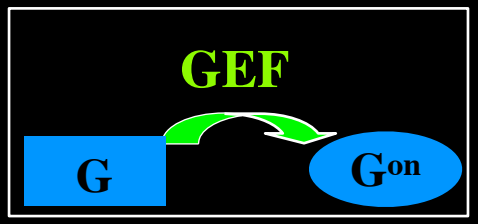
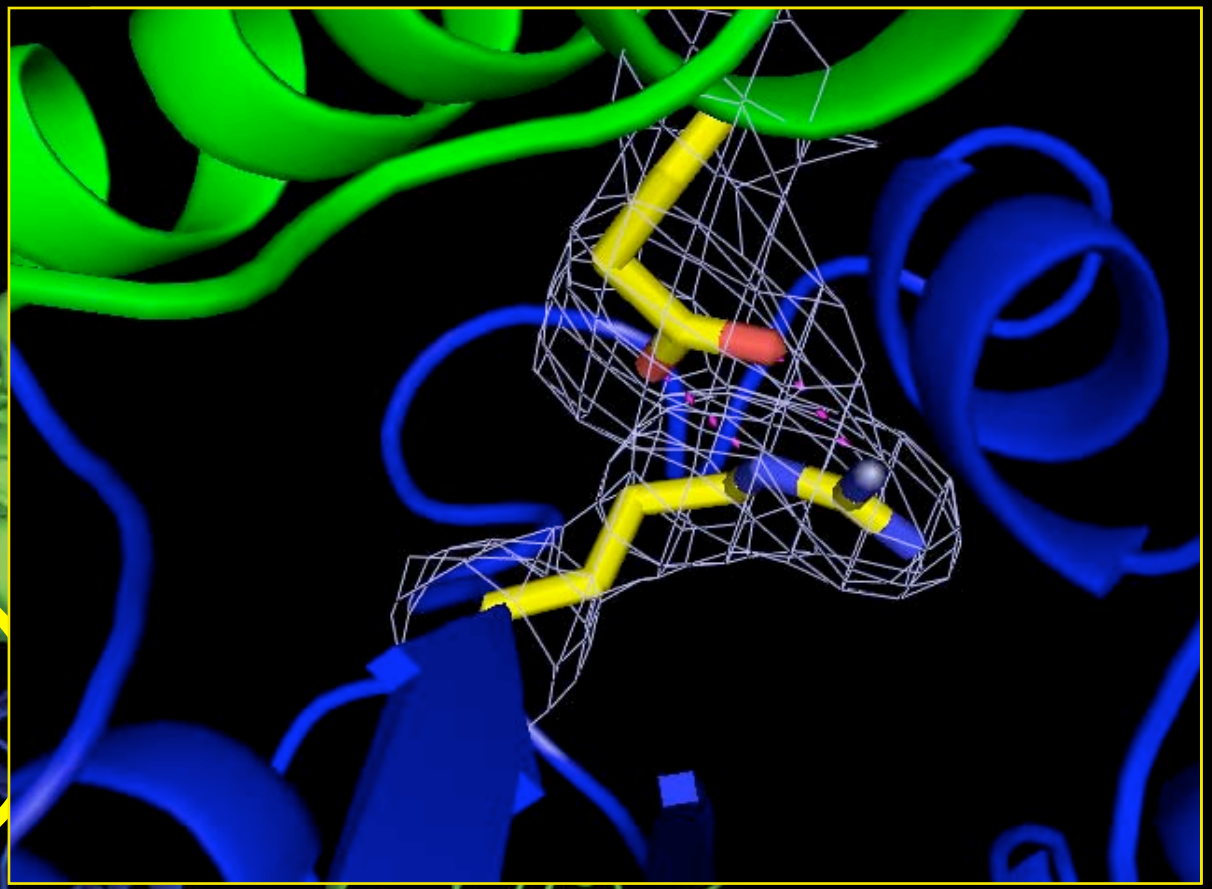




(X-ray)

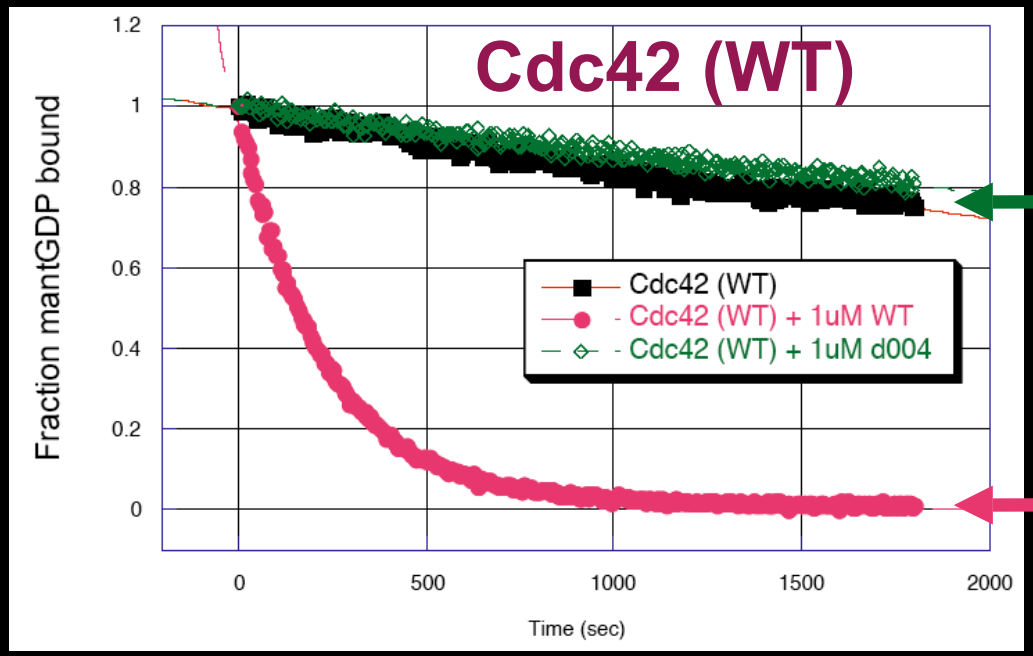
Cdc42

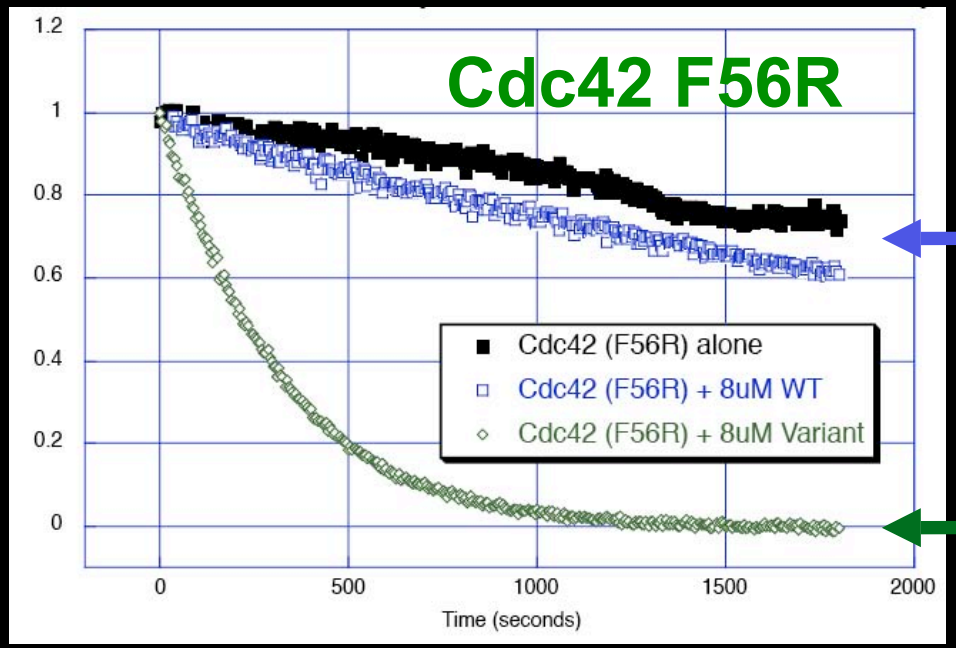
1KI1.pdb
Snyder et al. (2002) NSB v9 p468

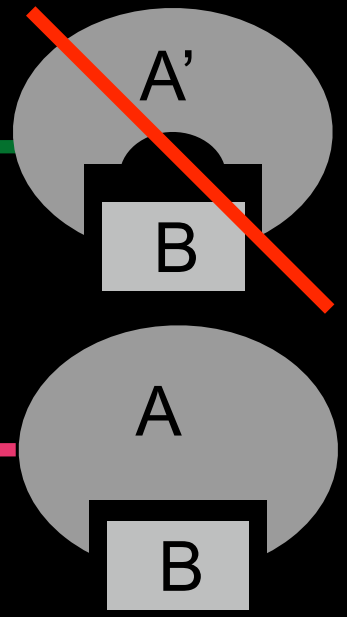
Greg Kapp

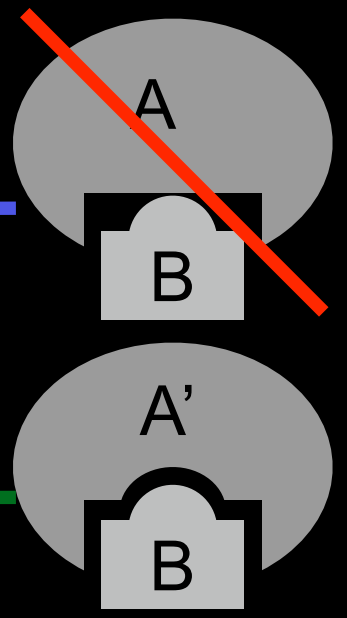
In vitro activity of a designed GTPase/GEF pair

Uncatalyzed (black) and GEF catalyzed (colours) dissociation of mantGDP monitored by fluorescence









Greg Kapp

OUTLINE

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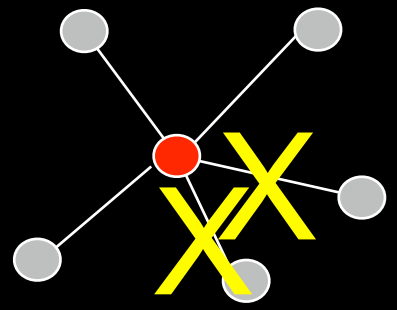

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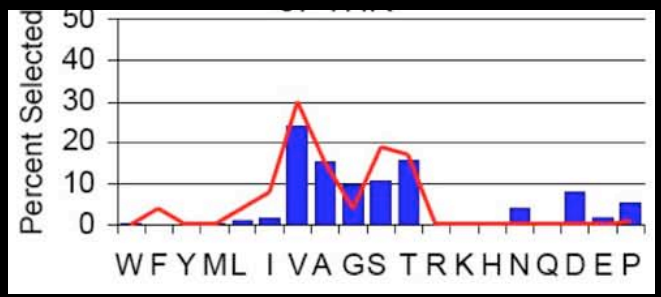

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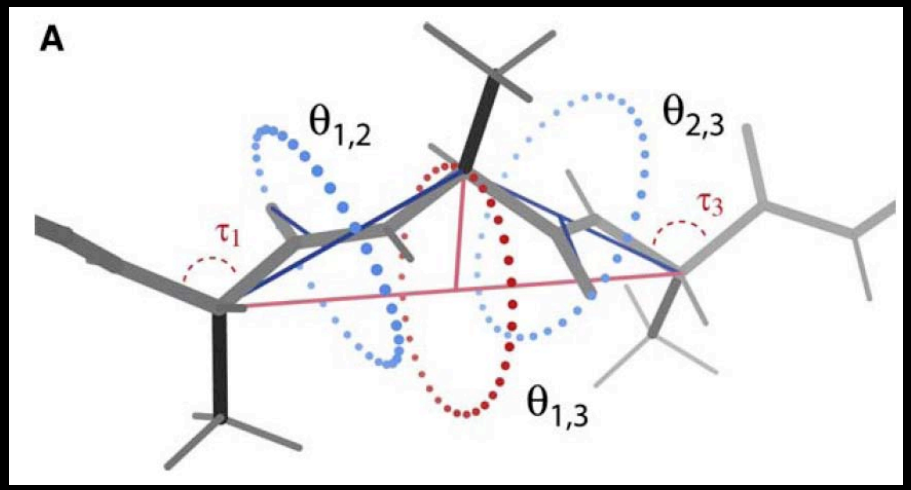
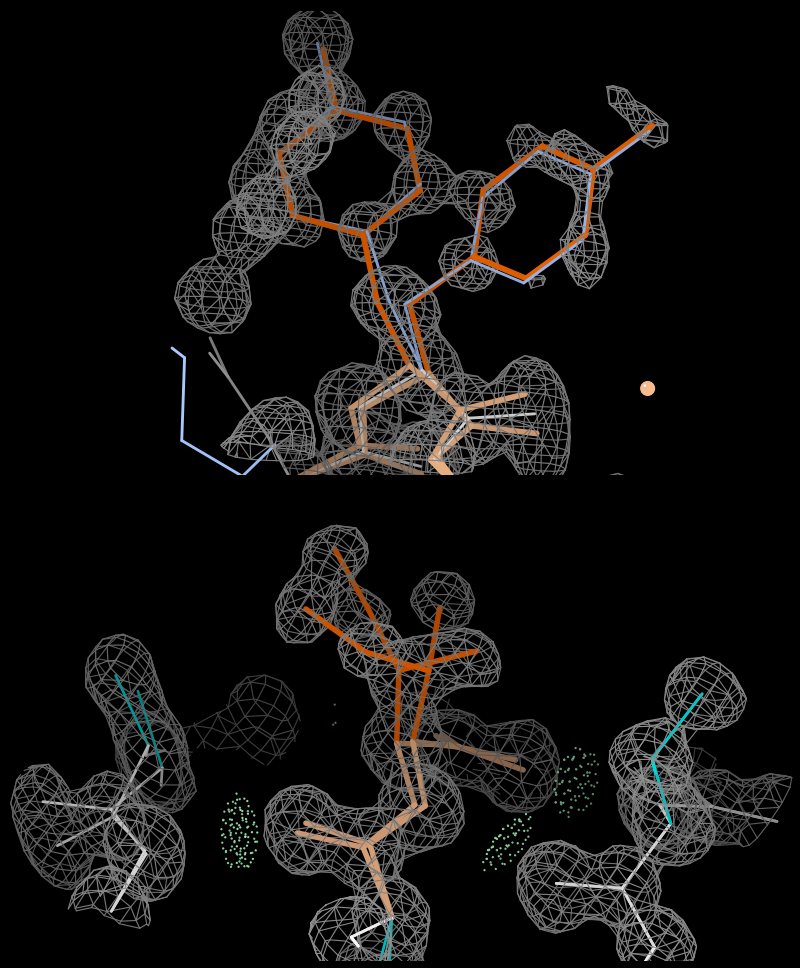
- *proteins can undergo conformational changes in response to mutation or binding their partners*
  - what are good models to capture conformational variability?
  - how do we test these?

Modeling backbone flexibility at high resolution

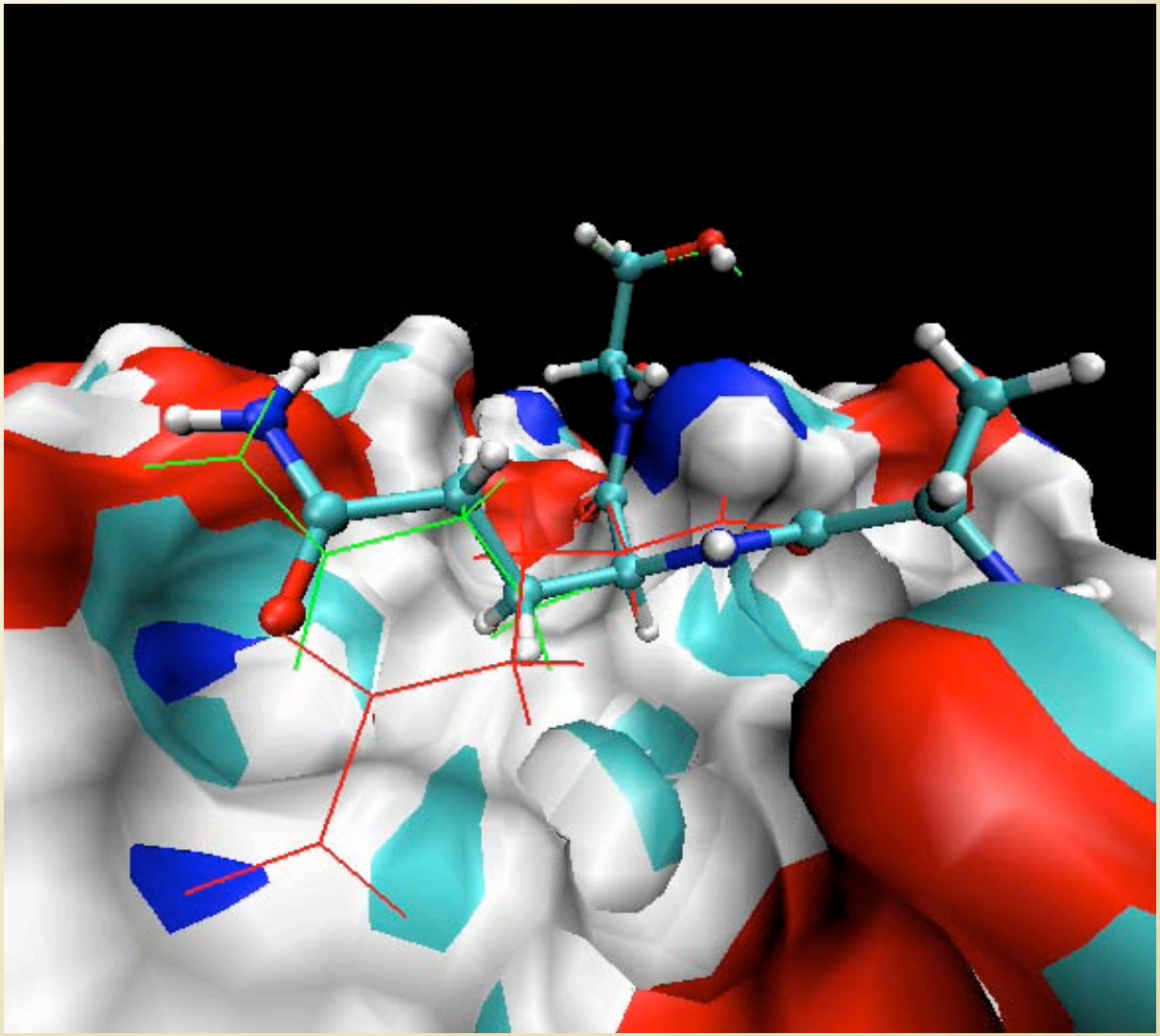
motivated by a paper by the Richardson lab/Ian Davis: “backrub” motion as a common type of local plasticity in the backbone (Davis *et al.*, Structure 2006)





Backrub simulation in rosetta

- coupled backbone/ rotamer motions



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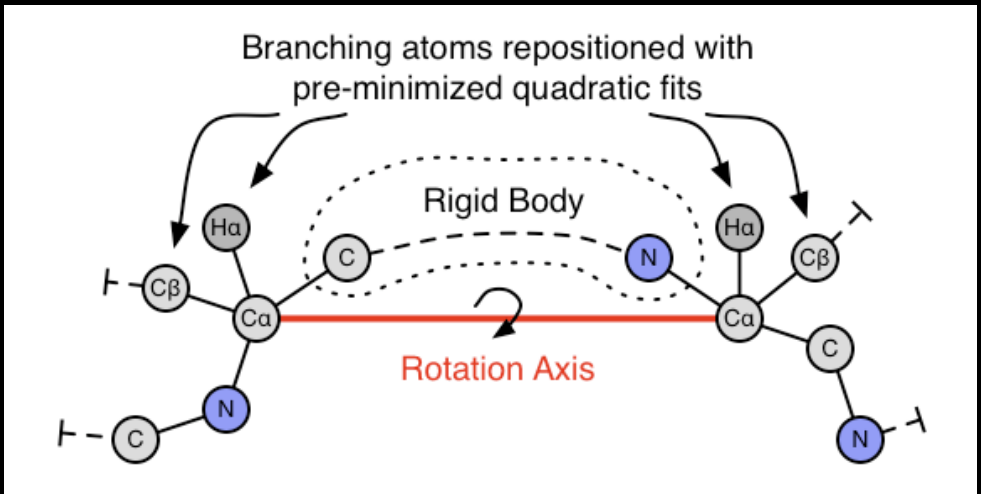
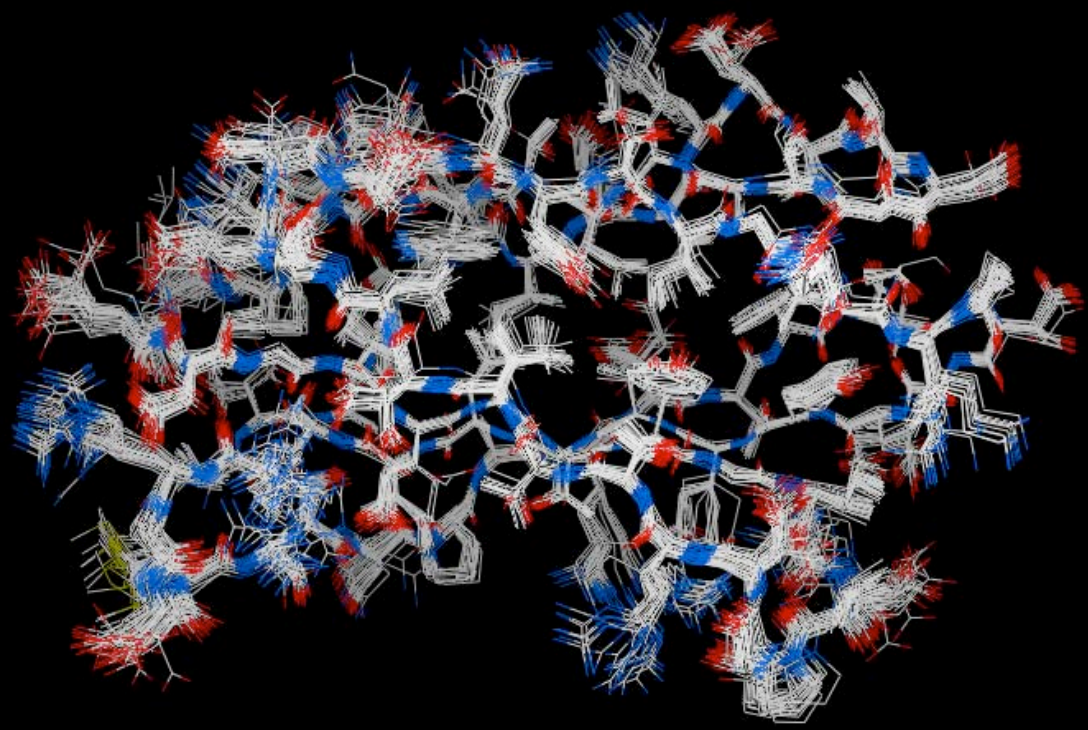
Modeling backbone flexibility at high resolution

generalized backrub (i,i+2 up to i,i+11) as ROSETTA Monte-Carlo move
(also for loop modeling)



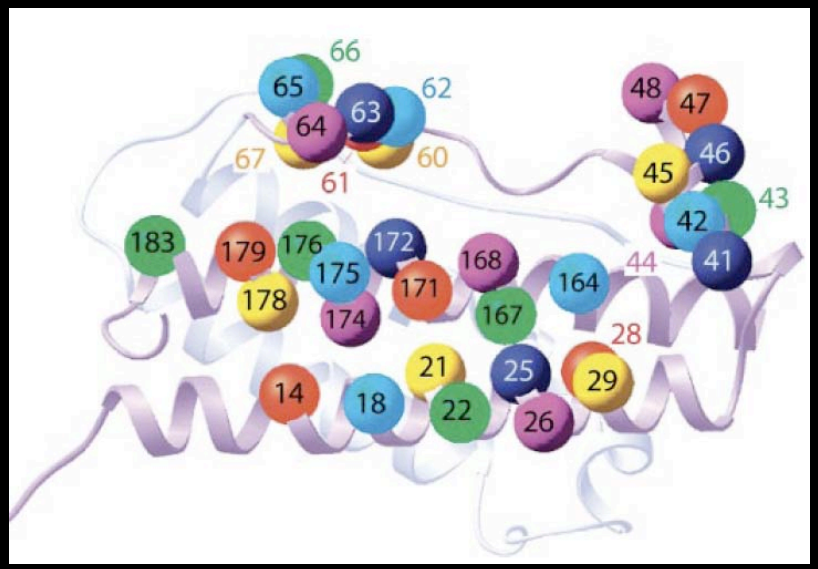


Colin Smith

Comprehensive and Quantitative Mapping of Energy Landscapes for Protein-Protein Interactions by Rapid Combinatorial Scanning*[S]◆

Received for publication, April 20, 2006, and in revised form, June 6, 2006 Published, JBC Papers in Press, June 8, 2006, DOI 10.1074/jbc.M603826200

Gábor Pál[‡1], Jean-Louis K. Kouadio[‡], Dean R. Artis[§], Anthony A. Kossiakoff[‡2], and Sachdev S. Sidhu[§3]

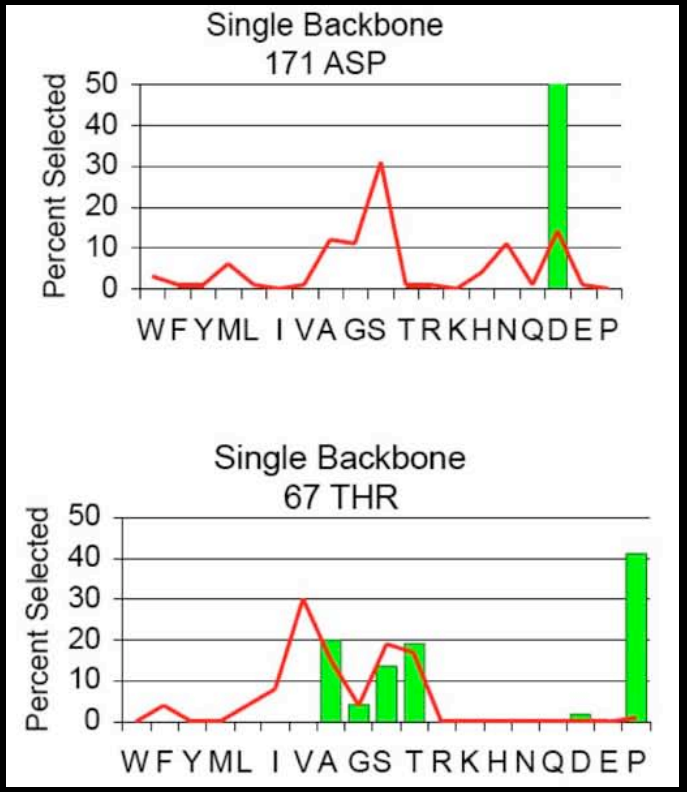


selection from comprehensive libraries for sets of 5-6 residues each
- for folding
- for receptor binding

major results:
- many substitutions tolerated
- patterns could not have been predicted from alignments

Predicting sets of tolerated sequences

HGH phage display results (*Pal et al., J. Biol. Chem. 2006*)



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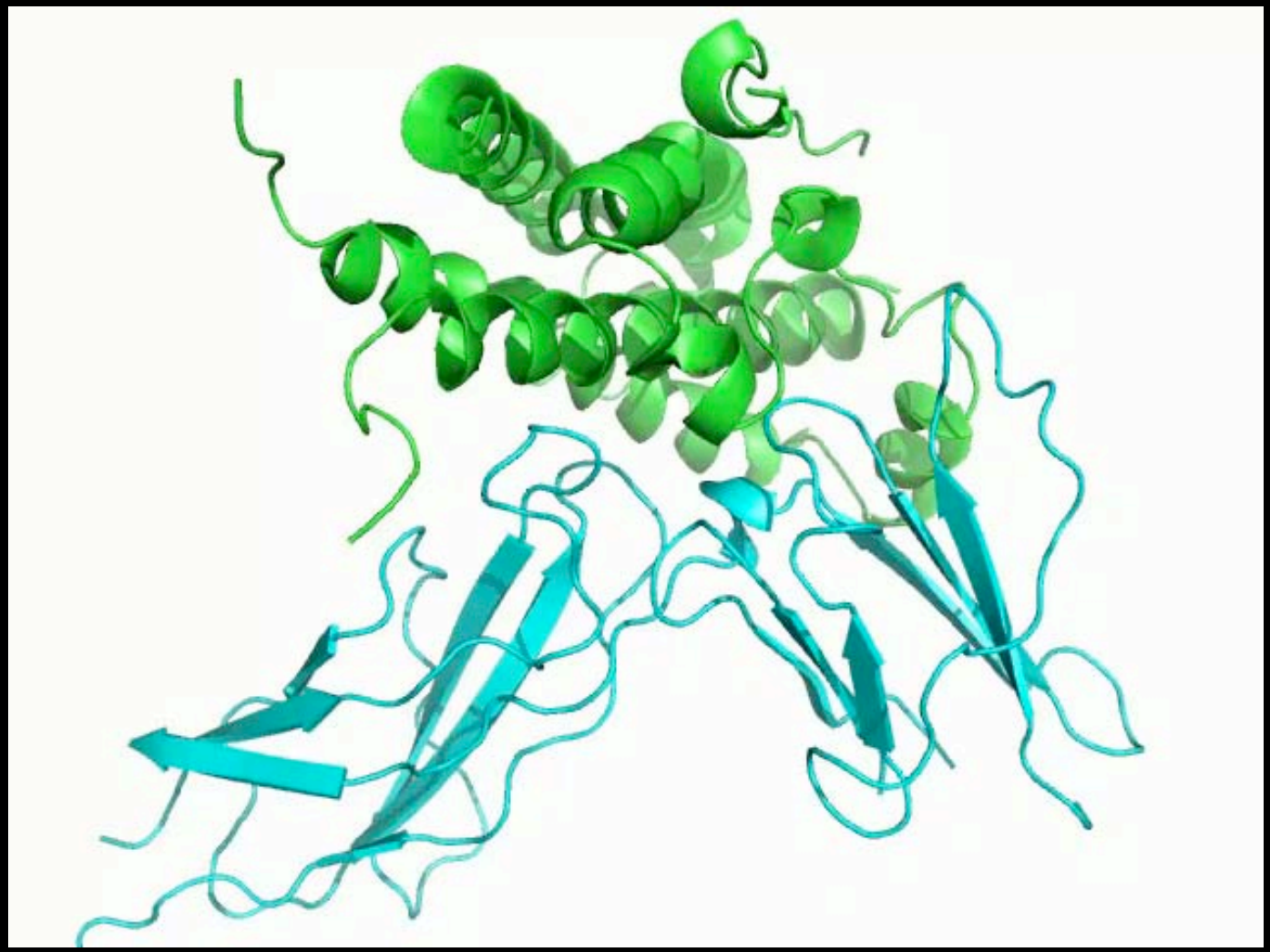
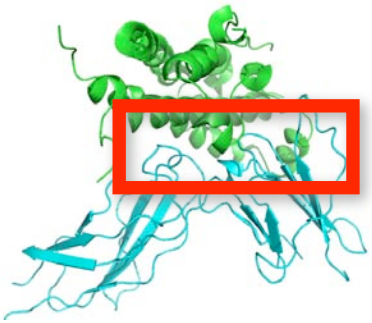
Ensemble of 170 backrub-generated structure



Compile Profiles for Each Backbone

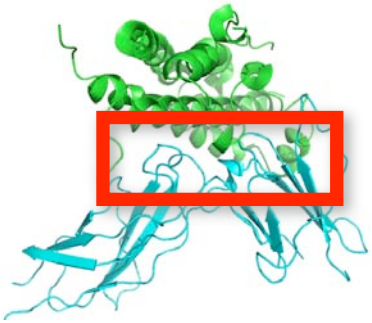
Everything Scoring "Better" Than Native



Backbone 1

….YGRVL…. -48.2

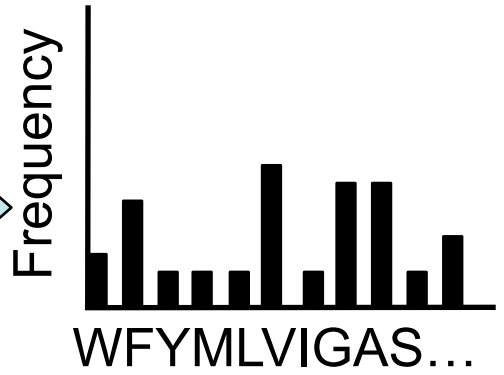
….FGKLV…. -49.6 4
….TASKM…. -45.3
….FGKLM…. -51.4 4
….YVRLM…. -46.3
….VVRKL…. -43.6
….LASKL…. -48.4 4

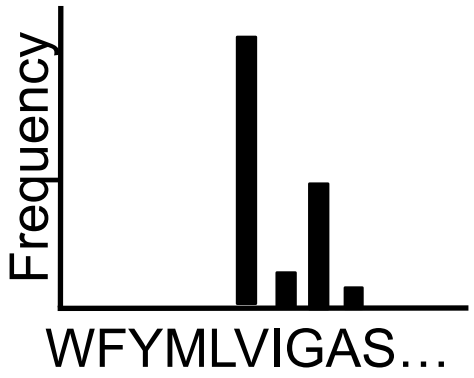


Backbone 2

….YGRVL…. -51.2

….SGKFM…. -46.2
….FASKM…. -52.1 4
….VGKLM…. -51.4 4
….VVRLM…. -52.9 4
….VVRKL…. -47.6
….SASKL…. -49.0



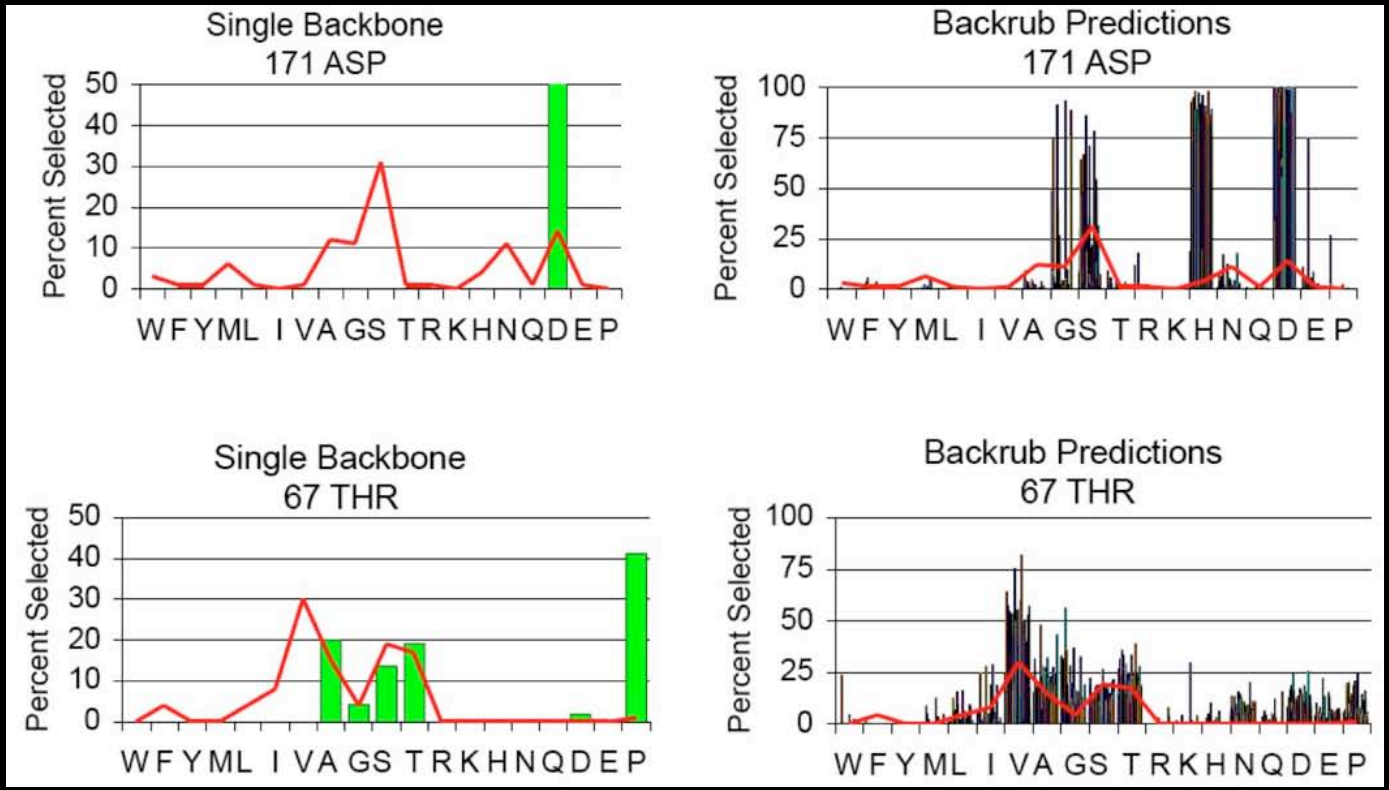


Cluster and Average

(Additional Threshold on Folding within 5% of wild type value)

Predicting sets of tolerated sequences

HGH phage display results (*Pal et al., J. Biol. Chem. 2006*)



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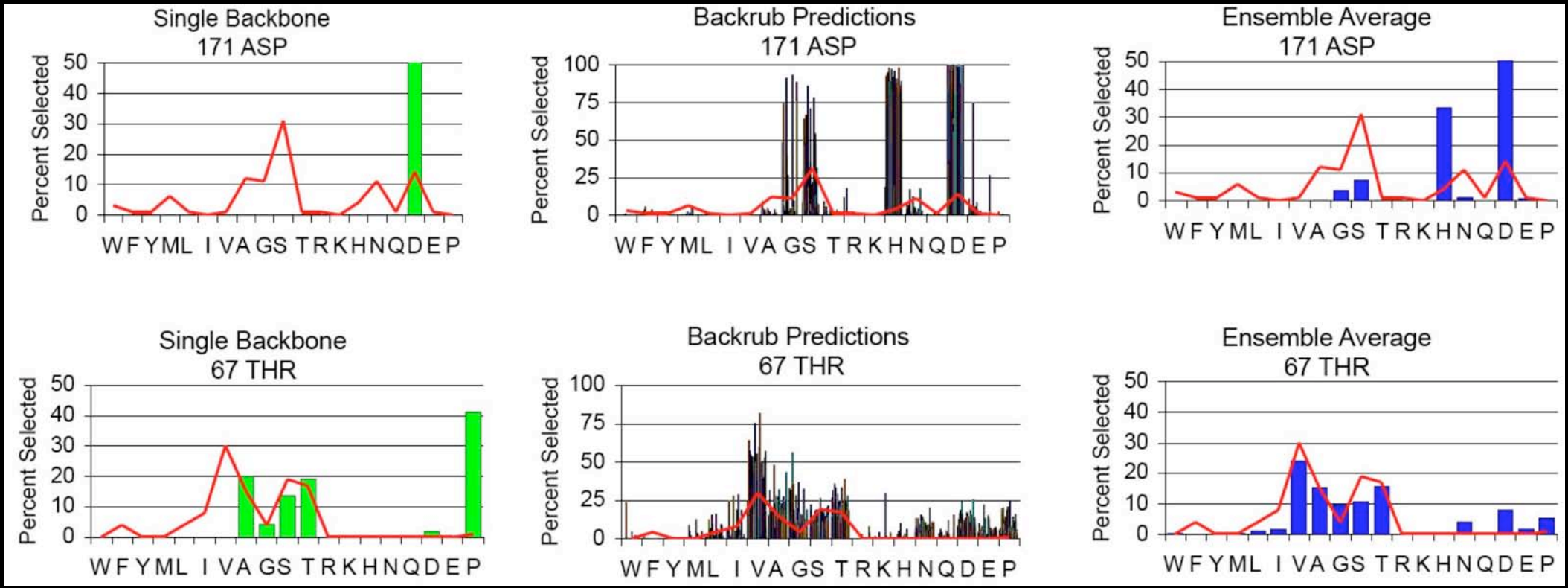

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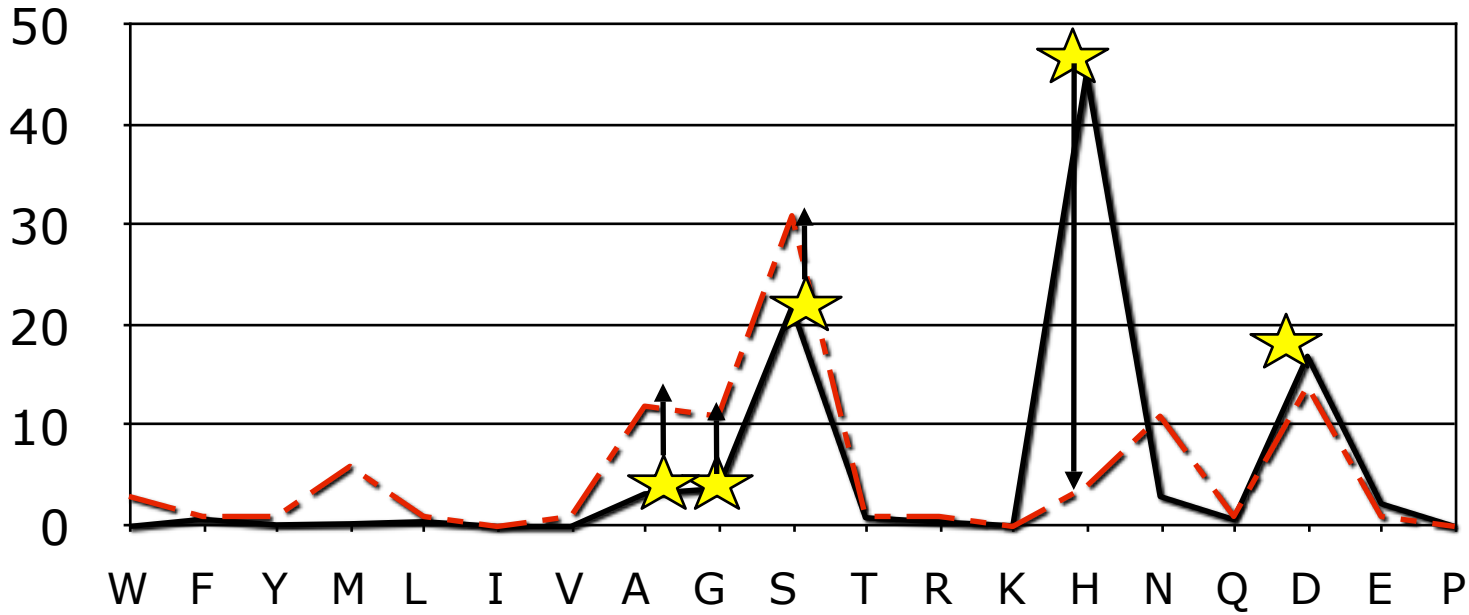
How well would computational predictions do for designing a library?

Pick 5 most frequent predicted amino acid types from each profile

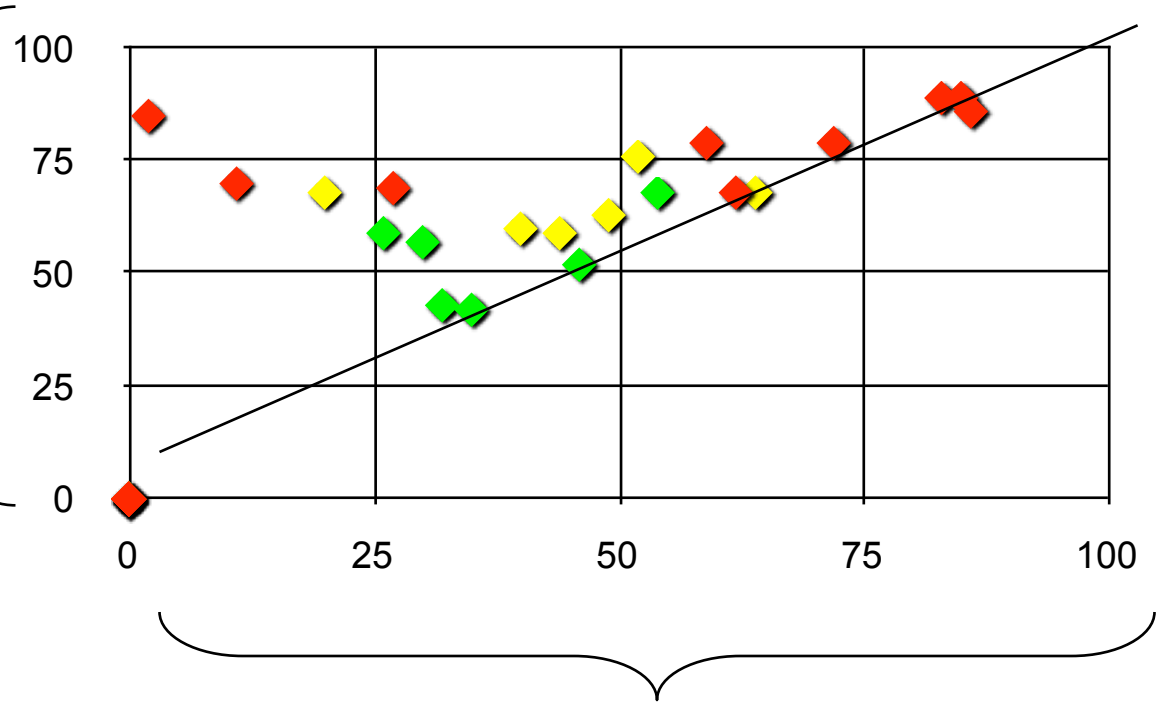


Computation: H, D, S, G, A 4+14+31+11+12 = 72

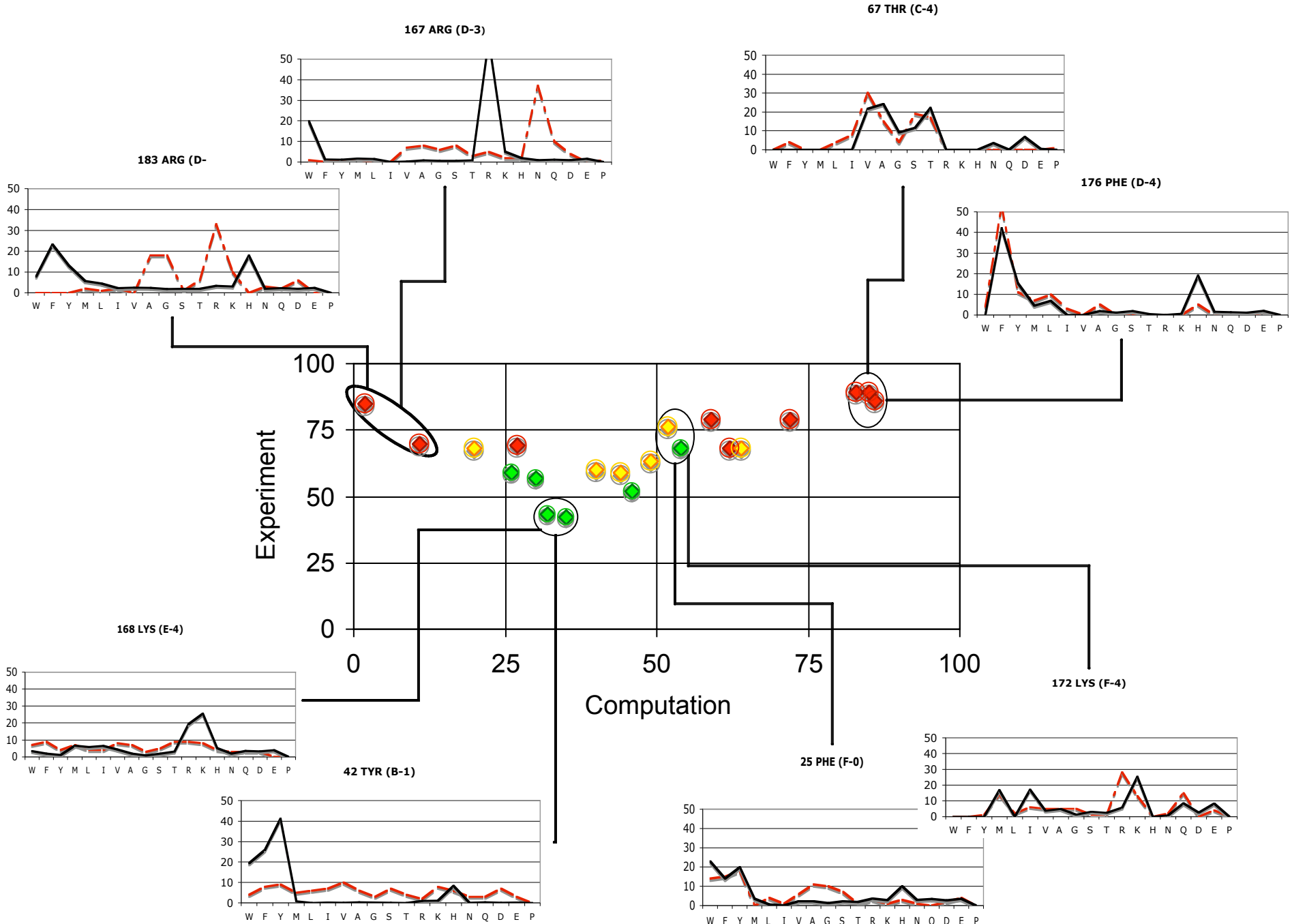
Max Seen: S, D, N, G, A 31+14 +12+11+11 = 79

Top 5 Residues Selected Computationally For Remaining 20 positions

Max % of sequences attainable by using only 5 residue types



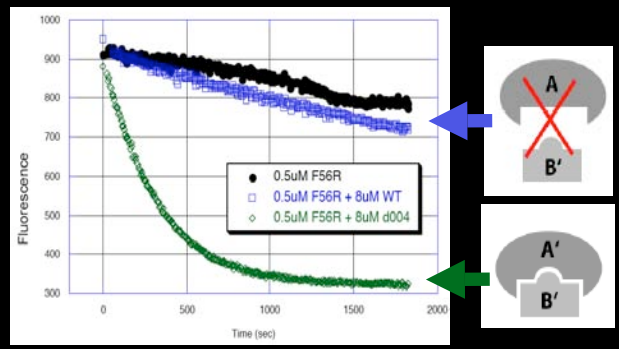
% of sequences expected to be recovered using computationally designed library (5 residues each position)


167 ARG (D-3)
67 THR (C-4)
183 ARG (D-
176 PHE (D-4)
168 LYS (E-4)
172 LYS (F-4)
42 TYR (B-1)
25 PHE (F-0)
Experiment
Computation
0
25
50
75
100
W F Y M L I V A G S T R K H N Q D E P

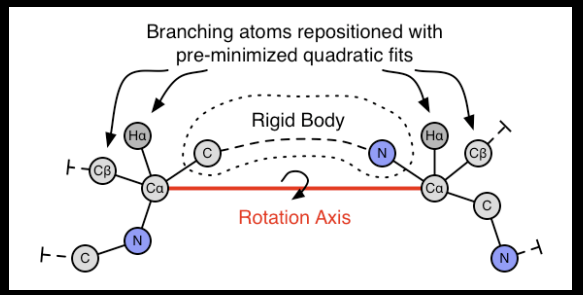
Conclusions

Reengineering sets of interactions

- GTPase/GEF pairs

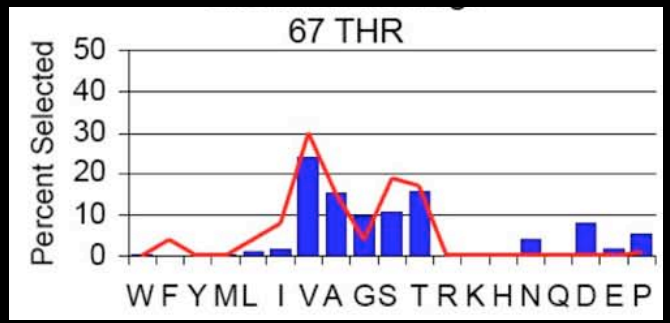


Backrub model for sampling local flexibility



Prediction of tolerated protein sequences using ensembles

- sequence plasticity & libraries



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