Anchor residues in protein-protein interactions

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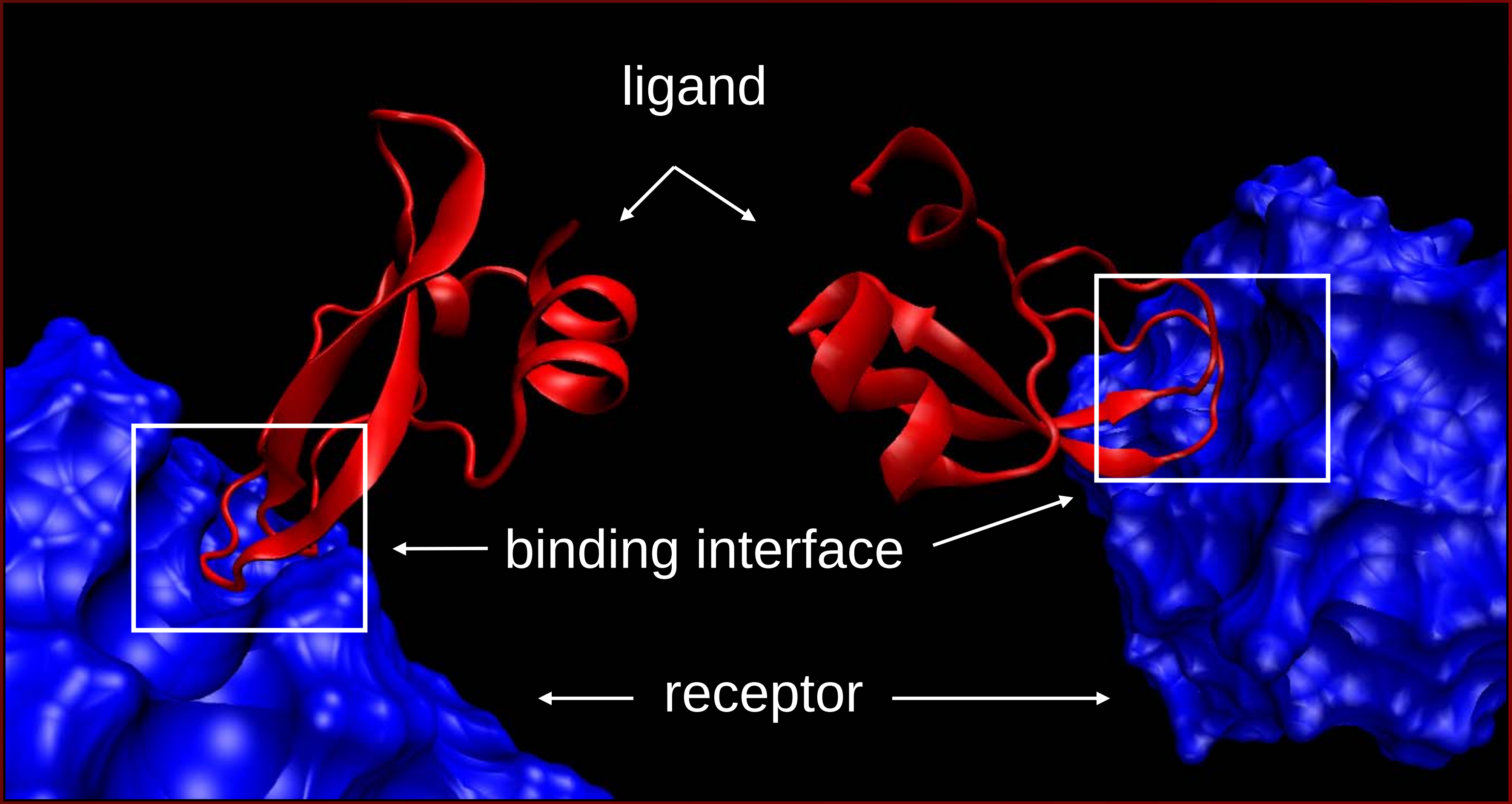
PNAS 2004

Anchor residues in protein-protein interactions

“. . protein interactions are critically dependent on just a few residues, or hot spots, at the binding interface.”

How do proteins bind to each other?



ligand

binding interface

receptor

How do binding proteins. . .?

- specifically recognize
- minimize kinetic costs
- maintain stability

Solution

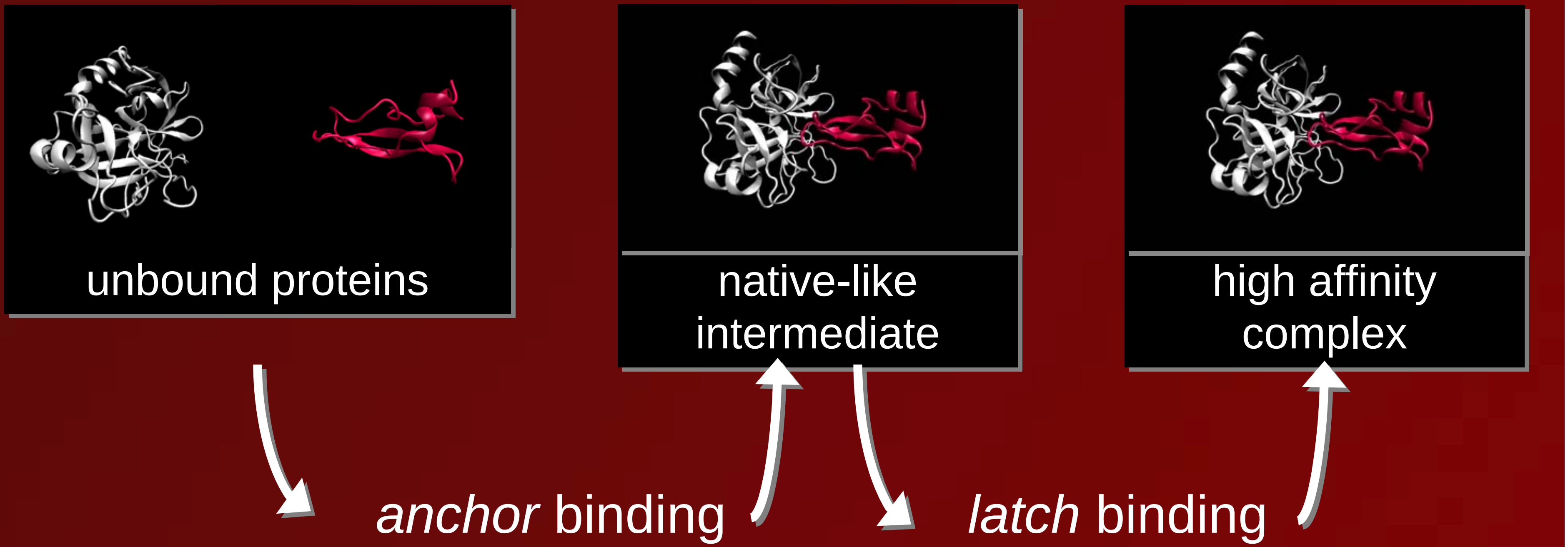
- *anchor* residues
- *latch* residues

Terms:

- solvent-accessible surface area

  $\Delta SASA^{\alpha} = SASA^{\alpha} - SASA^{\alpha\beta}$
- unbound vs. complex (bound) conformation
- native-like ~ bound-like
- native-like intermediate
- low affinity vs. high affinity
- “lock-and-key” (rigid) vs. “induced fit” (flexible)
- rotamer conformations

Association Model



unbound proteins

native-like intermediate

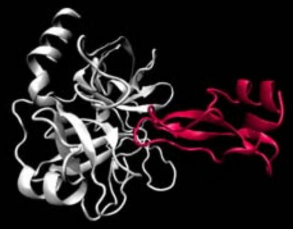
high affinity complex

anchor binding

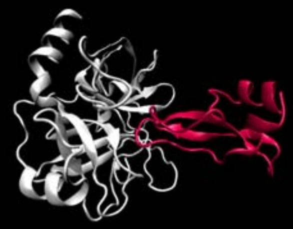
latch binding

Association Model

unbound proteins



native-like
intermediate



high affinity
complex

anchor binding

latch binding

ensures

specific *recognition*

specific *stability*

interface core
= solvent inaccessible

binding location

interface periphery
= solvent accessible

Procedure

- Identified anchor residues in protein-protein complexes (interface core)

- Compared MD-simulated conformations (unbound) to bound

- Identified latch residues at (interface periphery)

Identifying (defining) anchors

- fully buried after binding
- largest $\Delta SASA$ value
- generally on ligand surface

geometry

- mostly polar or charged group: Arg, Lys etc.

chemistry

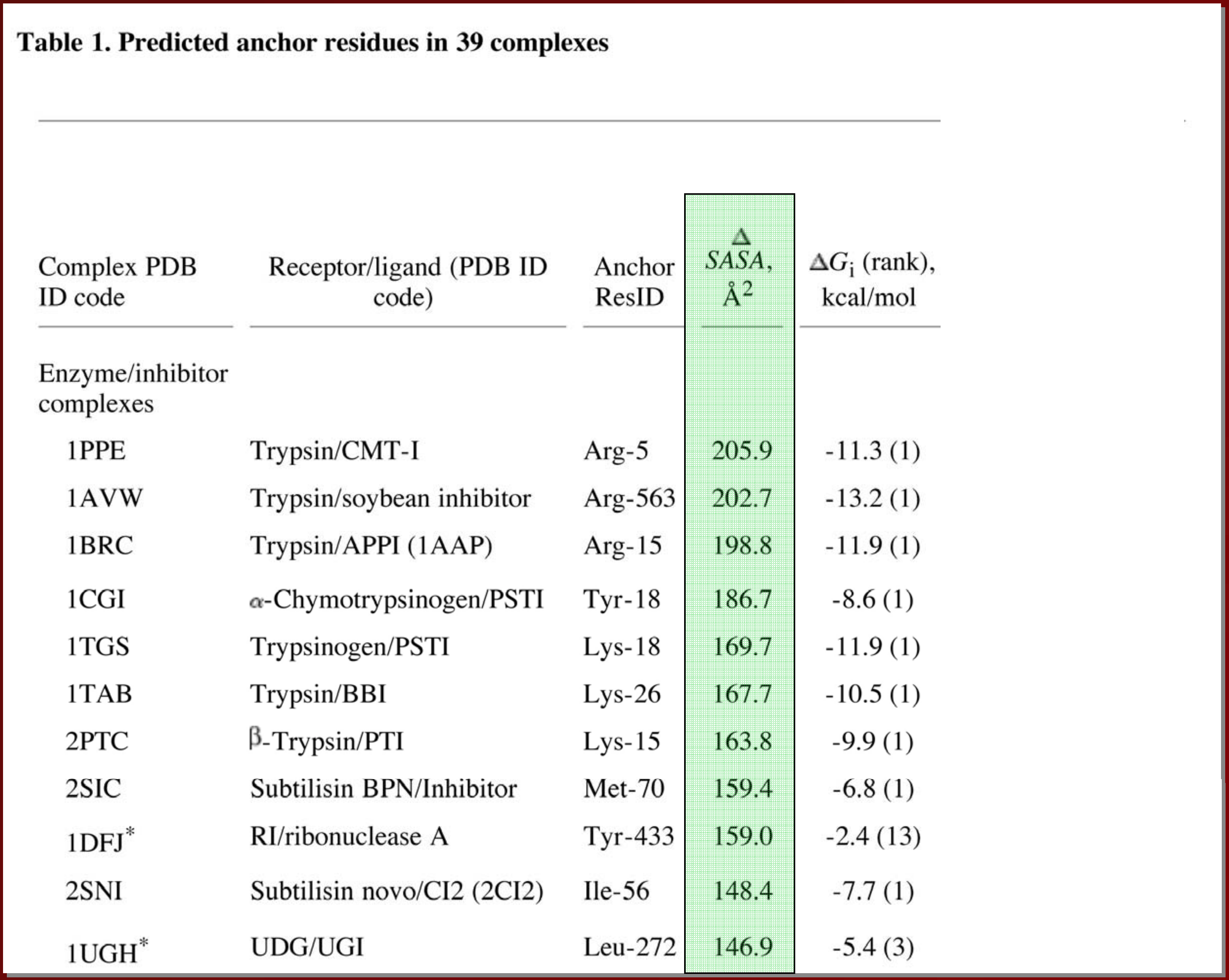
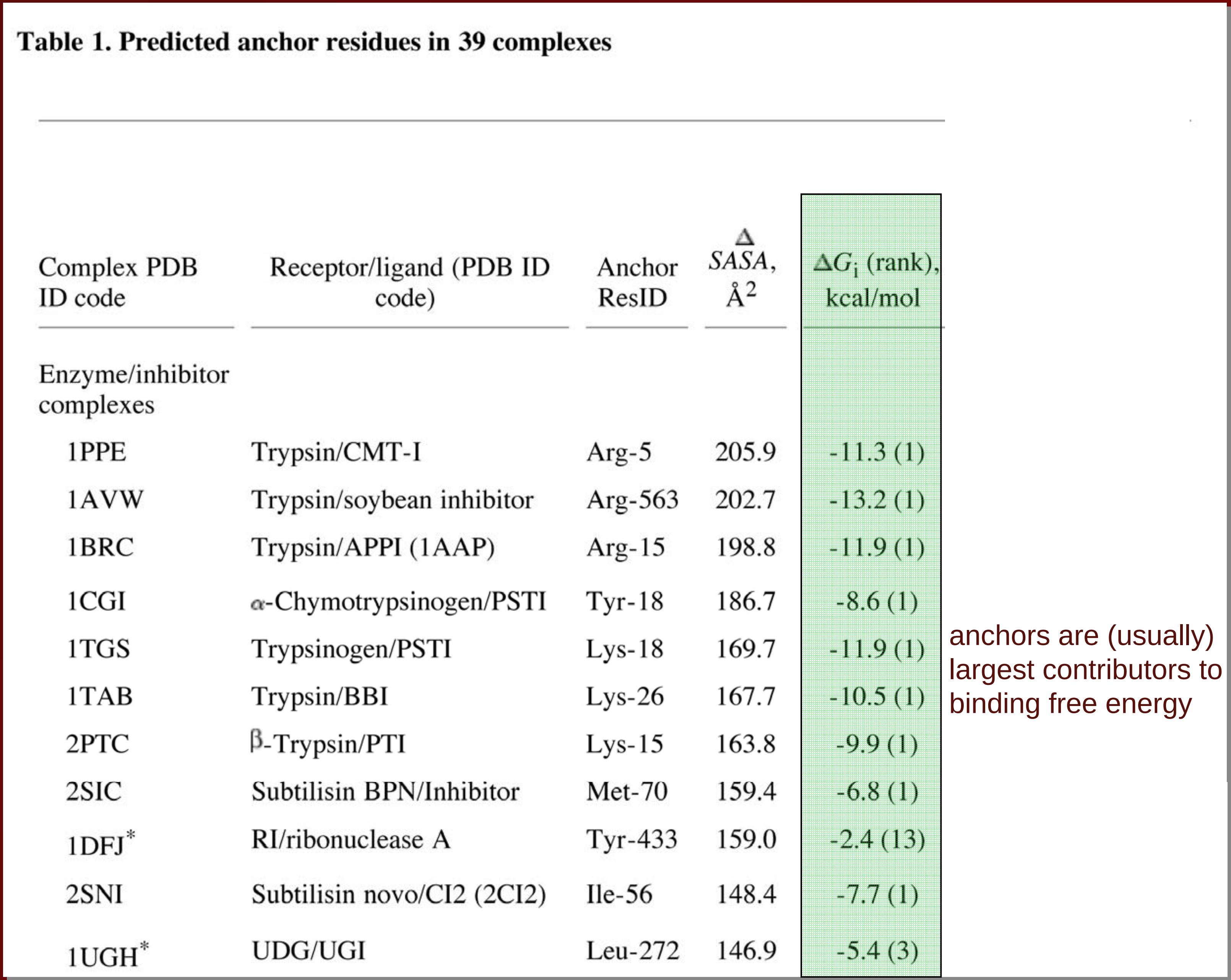


Table 1. Predicted anchor residues in 39 complexes

Complex PDB ID code	Receptor/ligand (PDB ID code)	Anchor ResID	Δ *SASA*, Å^2	ΔG_{i} (rank), kcal/mol
Enzyme/inhibitor complexes				
1PPE	Trypsin/CMT-I	Arg-5	205.9	-11.3 (1)
1AVW	Trypsin/soybean inhibitor	Arg-563	202.7	-13.2 (1)
1BRC	Trypsin/APPI (1AAP)	Arg-15	198.8	-11.9 (1)
1CGI	α-Chymotrypsinogen/PSTI	Tyr-18	186.7	-8.6 (1)
1TGS	Trypsinogen/PSTI	Lys-18	169.7	-11.9 (1)
1TAB	Trypsin/BBI	Lys-26	167.7	-10.5 (1)
2PTC	β-Trypsin/PTI	Lys-15	163.8	-9.9 (1)
2SIC	Subtilisin BPN/Inhibitor	Met-70	159.4	-6.8 (1)
1DFJ*	RI/ribonuclease A	Tyr-433	159.0	-2.4 (13)
2SNI	Subtilisin novo/CI2 (2CI2)	Ile-56	148.4	-7.7 (1)
1UGH*	UDG/UGI	Leu-272	146.9	-5.4 (3)



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anchors are (usually) largest contributors to binding free energy

closer look at two identified anchors

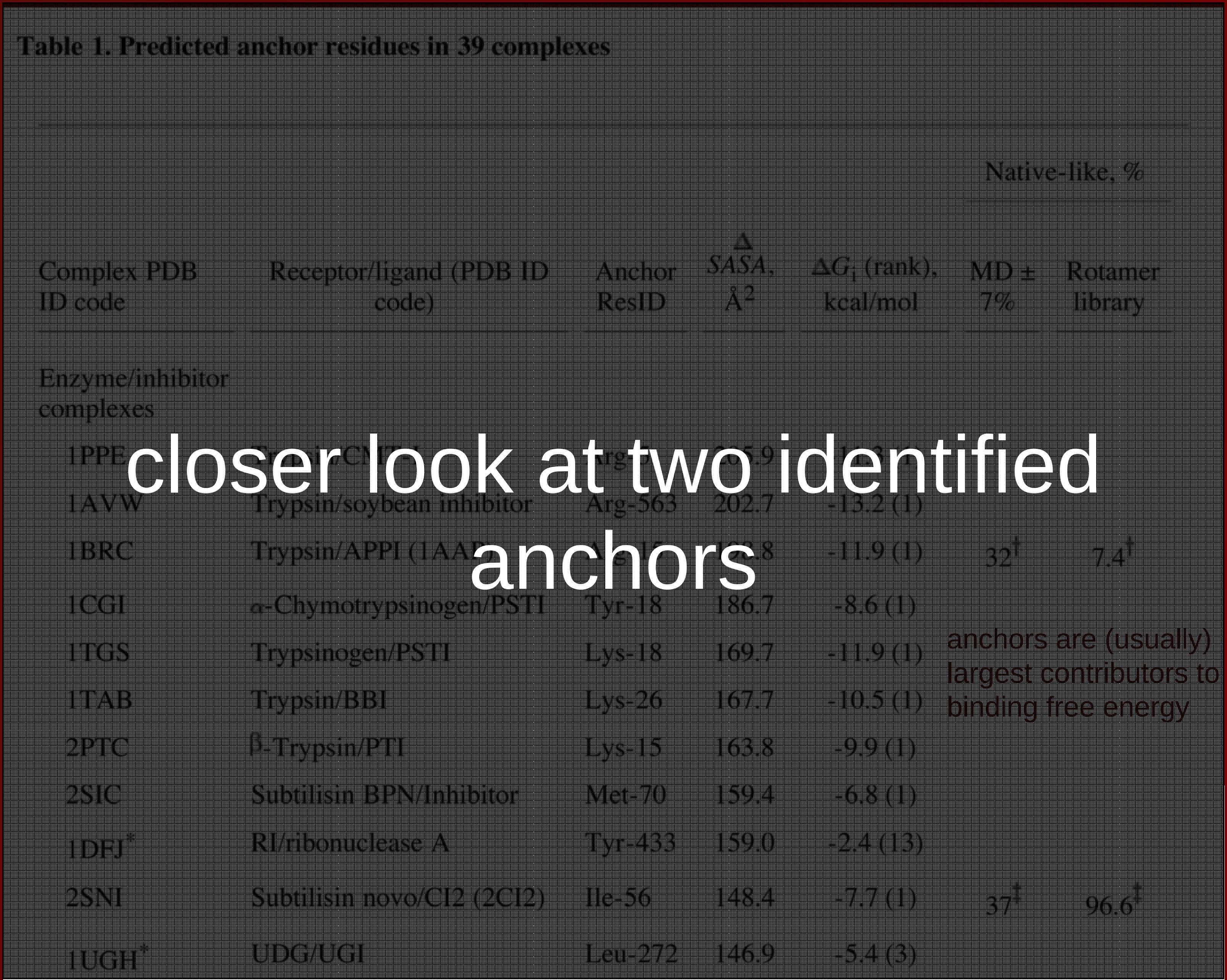

Table 1. Predicted anchor residues in 39 complexes

Complex PDB ID code	Receptor/ligand (PDB ID code)	Anchor ResID	Δ *SASA*, Å^2	ΔG_1 (rank), kcal/mol	Native-like, % MD ± 7%	 Rotamer library
Enzyme/inhibitor complexes						
1PPE	[illegible]CMTI-I	Arg-[illegible]	[illegible]5.9	[illegible]		
1AVW	Trypsin/soybean inhibitor	Arg-563	202.7	-13.2 (1)		
1BRC	Trypsin/APPI (1AA[illegible]	[illegible]-15	[illegible].8	-11.9 (1)	32†	7.4†
1CGI	α-Chymotrypsinogen/PSTI	Tyr-18	186.7	-8.6 (1)		
1TGS	Trypsinogen/PSTI	Lys-18	169.7	-11.9 (1)		
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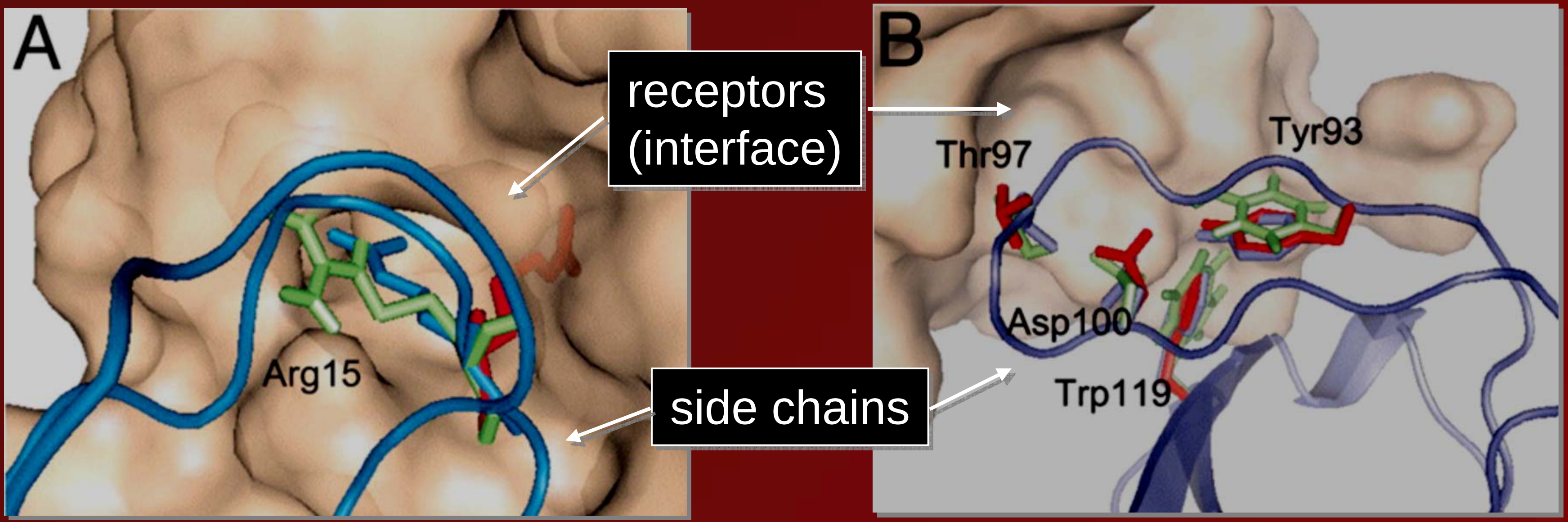
1DFJ*	RI/ribonuclease A	Tyr-433	159.0	-2.4 (13)		
2SNI	Subtilisin novo/CI2 (2CI2)	Ile-56	148.4	-7.7 (1)	37‡	96.6‡
1UGH*	UDG/UGI	Leu-272	146.9	-5.4 (3)		

anchors are (usually) largest contributors to binding free energy



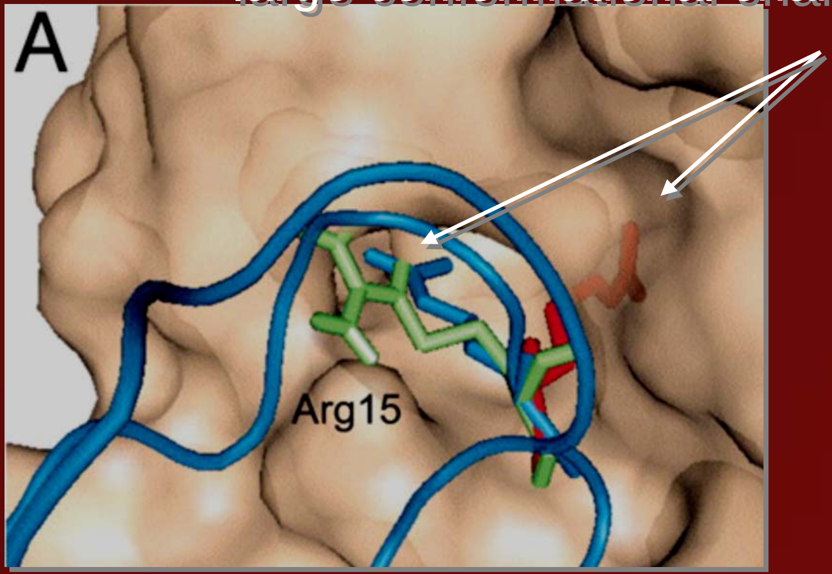
receptors (interface)

side chains

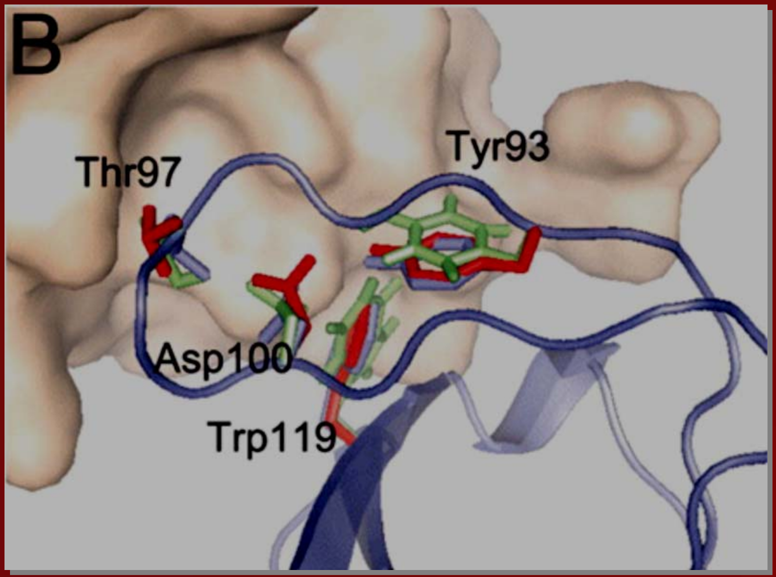
- Receptors (large) are surface rep.
- Protein (ligand) side chains are cartoon rep.
- Anchors are in stick form

    blue = complex crystal structure
    red = unbound crystal structure
    green = most common simulation conformation

large conformational change?



trypsin/amyloid β-protein inhibitor



tyrosine kinase SH3

- single anchor residue (Δ*SASA* > 100 Å^2) - bound-unbound structural change	- native structure resembles unbound conformation - inflexible - multiple residues have significant Δ*SASA* (< 100 Å^2)

blue = complex red = unbound green = simulation

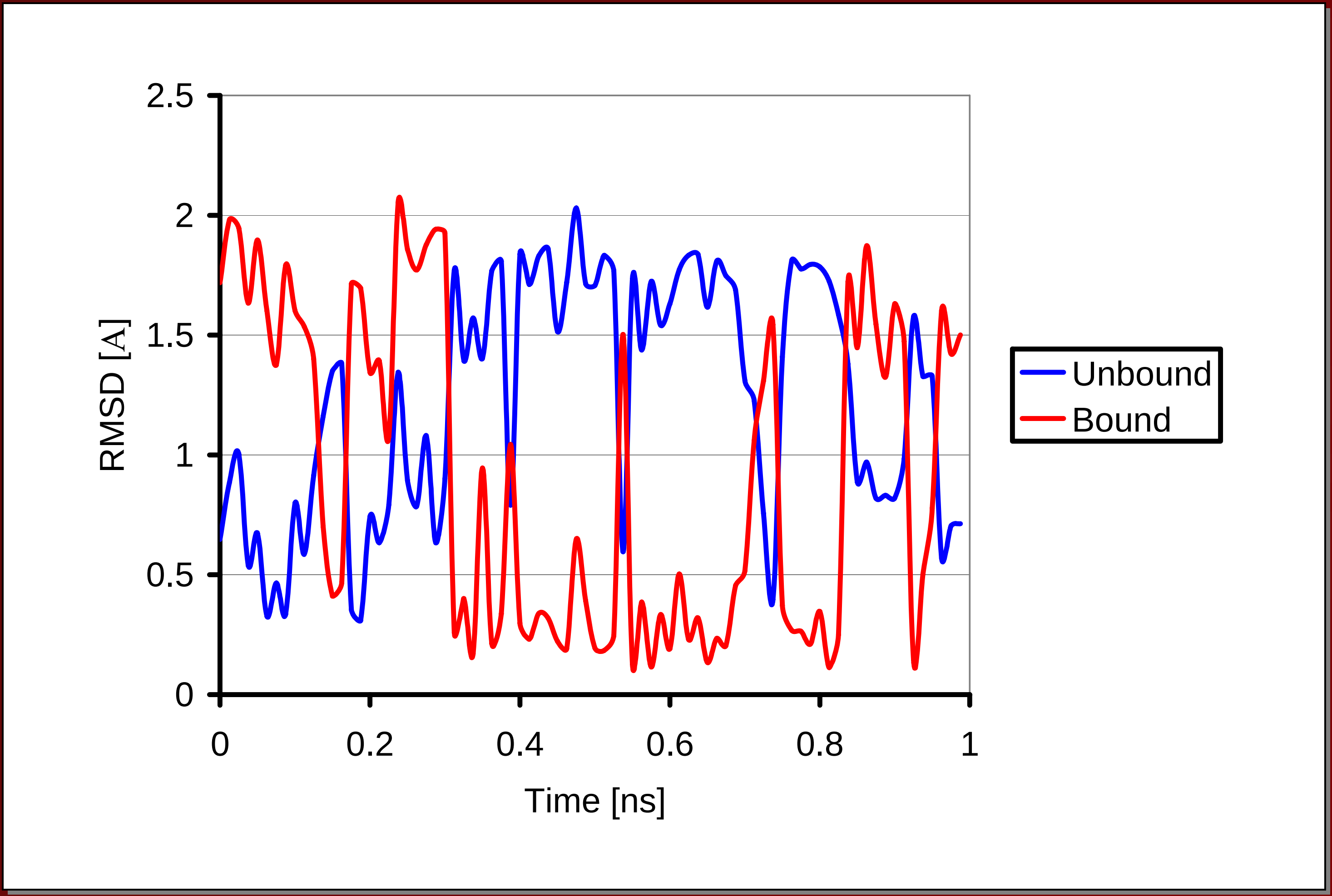
Outline

- Identified anchor residues in protein-protein complexes

- Compared MD-simulated conformations (unbound) to bound

- Identified latch residues at binding periphery

MD simulation



Outline

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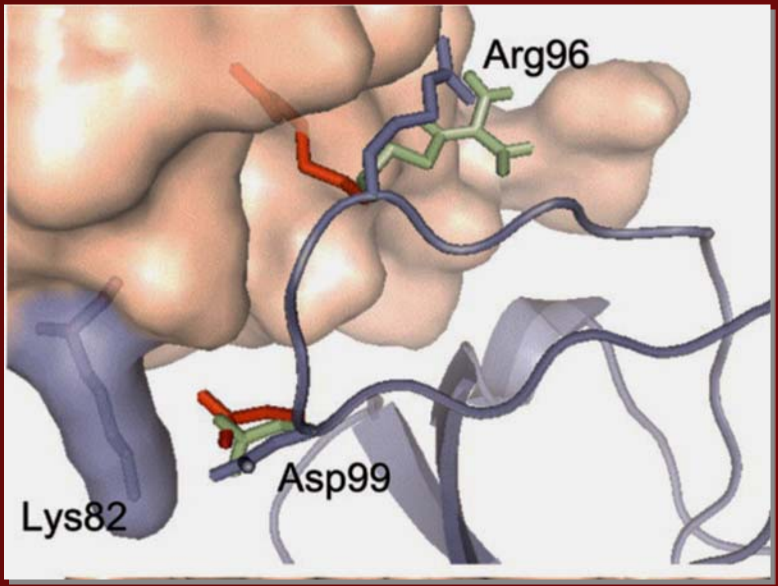
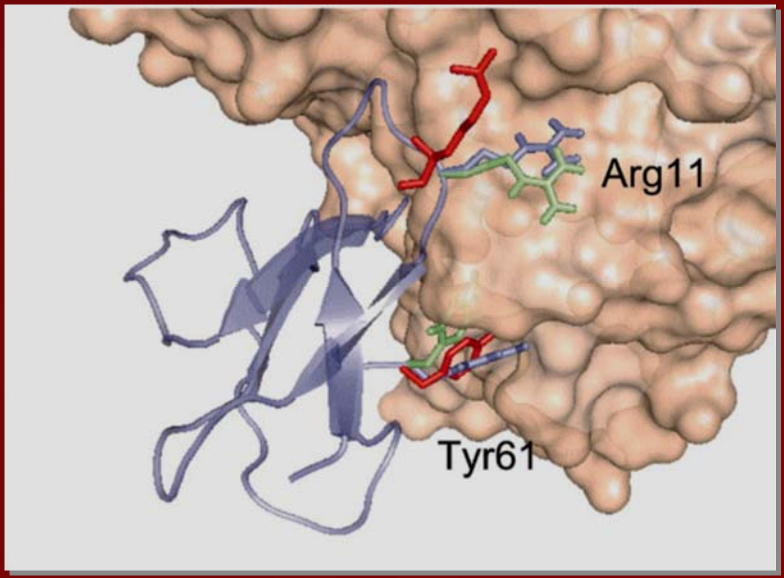
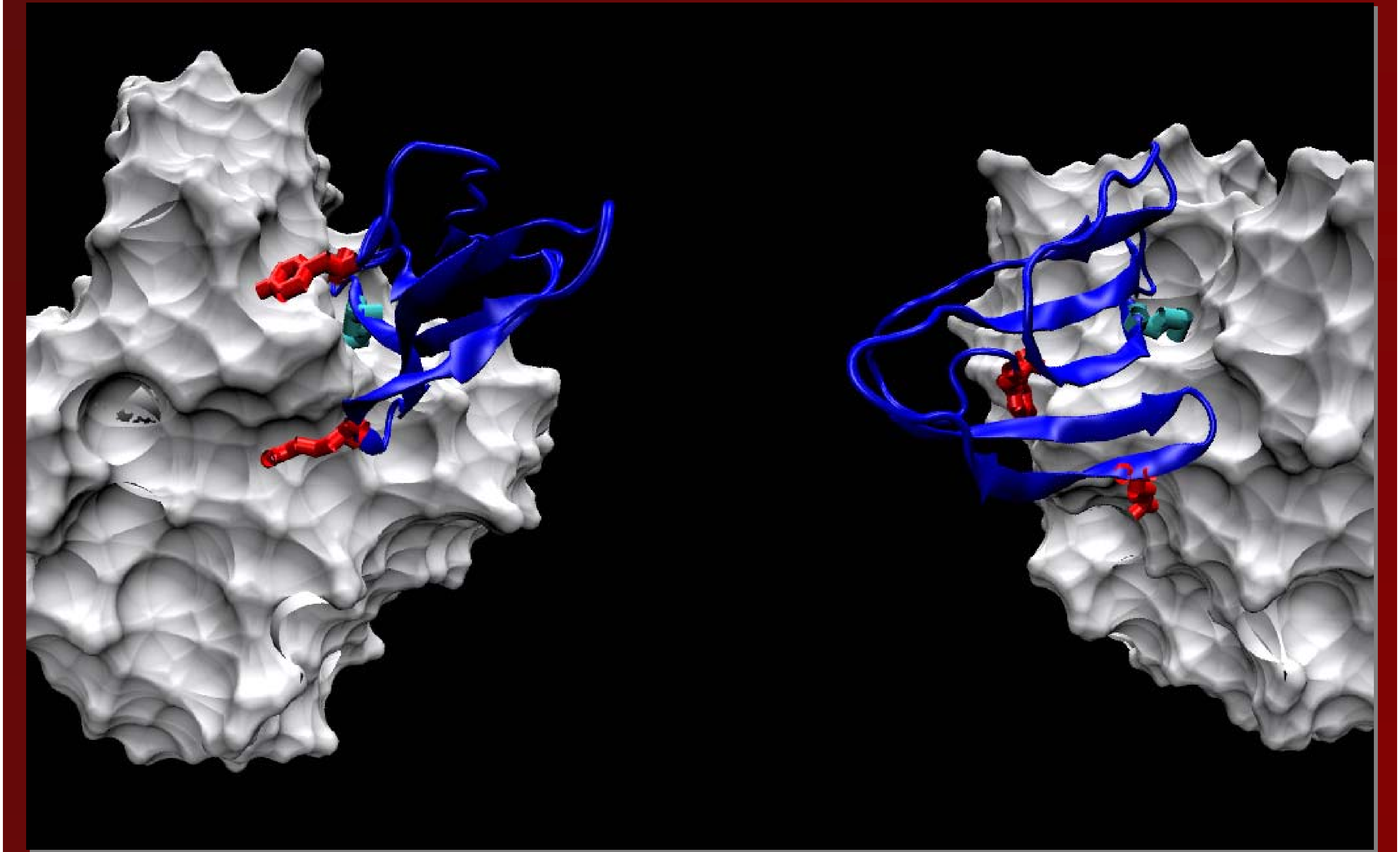
Latches

- lock complex after encounter complex formation
- “relatively free to adjust” → flexible-flexible pair → flexible-rigid pair
- 30-60% buried
- on either molecule





Lock and Key AND Induced Fit



Conclusions

- bumpy interface
- specificity and recognition by anchors
- large Δ*SASA* = few secondary anchors
- high affinity (stability) by latch side chains