Chris Garcia, Ph.D
kcgarcia@stanford.edu

Protein-Protein Interactions - I

-Proteins form highly specific and stable complexes with other proteins and/or ligands.

-Protein interactions mediate vast majority of biological processes.

- e.g. cell-surface receptor-ligand interactions.

-Come in many sizes, shapes, chemical and energetic content which are unique to each interaction (is there a *protein recognition code* ?).

-Although we are getting better at predicting structure from sequence, an elusive goal remains to predict interactions from structure.

-**Despite the diverse biological origins, all protein interactions are mediated by a common set of physical principles.**

-at a microscopic level, protein binding and enzymatic catalysis can be described by the same underlying chemical principles as protein folding.

-Binding proteins have evolved to form stable, long-lived interactions with partners. Enzymes have evolved to form transient interactions to enable rapid turnover.

-however, some of the macroscopic descriptors differ.

Our goals for the next two lectures are to understand:

- What is a *protein-protein interface* ?
- What is a *binding site* ?
- How can we describe a *protein-protein interface* qualitatively and quantitatively?
- How do we experimentally dissect protein-protein interfaces ?
- Can we use principles of protein interactions to engineer protein interfaces ?

assigned reading: J. Janin. Angstroms and calories. *Structure*. 1997, 5(4):473-9.

Protein-Protein Interactions - I

Lecture contents:

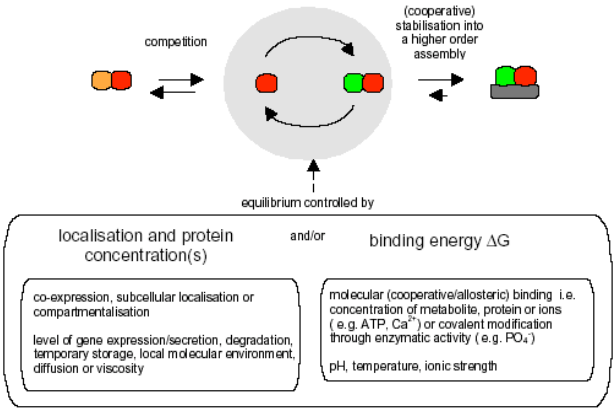
describe
- I. Taxonomy
- A. Obligate vs. Non-obligate
- B. Surface area.
- C. Shape complementarity.
- D. Chemical complementarity.
  - 1) Charge.
  - 2) H-Bond
  - 3) VDW
  - 4) Hydrophobic

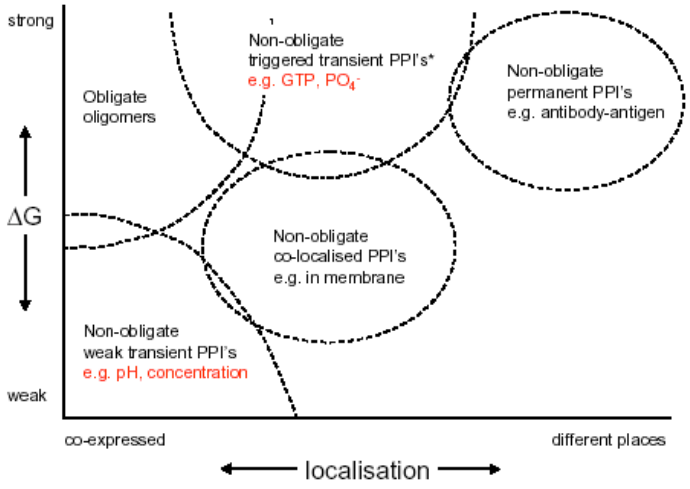
analyze
- E. Comprehensive analysis and prediction.

predict
- II. Structural energetics.

I. Taxonomy

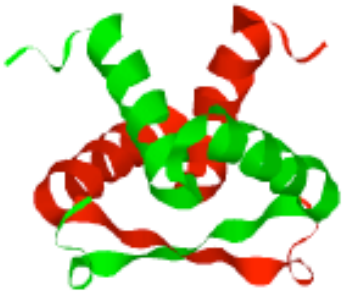
A) Obligate versus non-obligate complexes (JM Thornton, 2002).



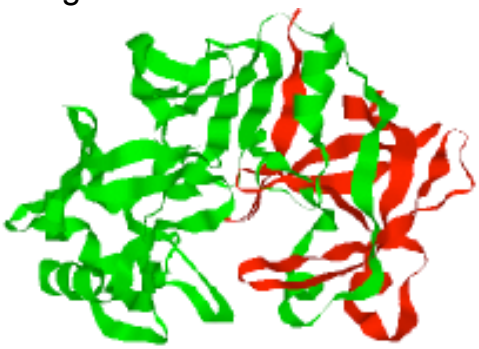


A gallery of various protein-protein complexes:

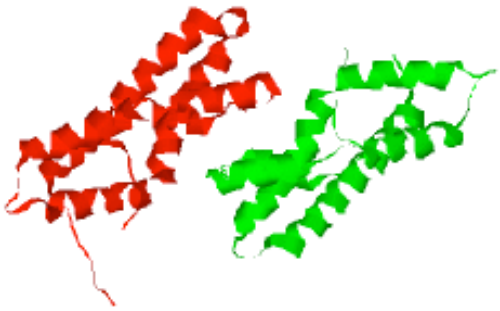
obligate homodimer: P22 Arc repressor



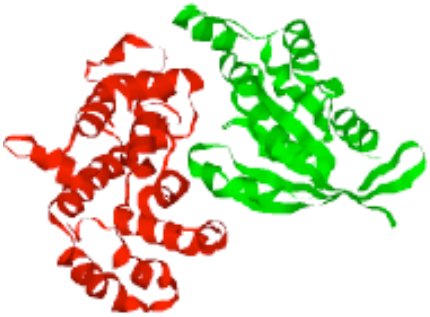
obligate heterodimer: human cathepsin D



non-obligate homodimer: sperm lysin

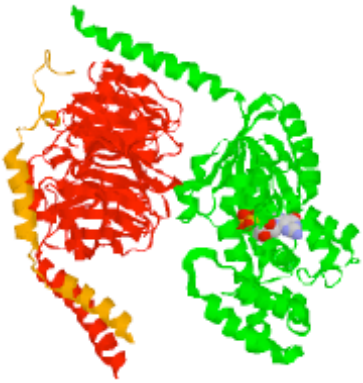


non-obligate heterodimer:
RhoA-RhoGAP signalling complex

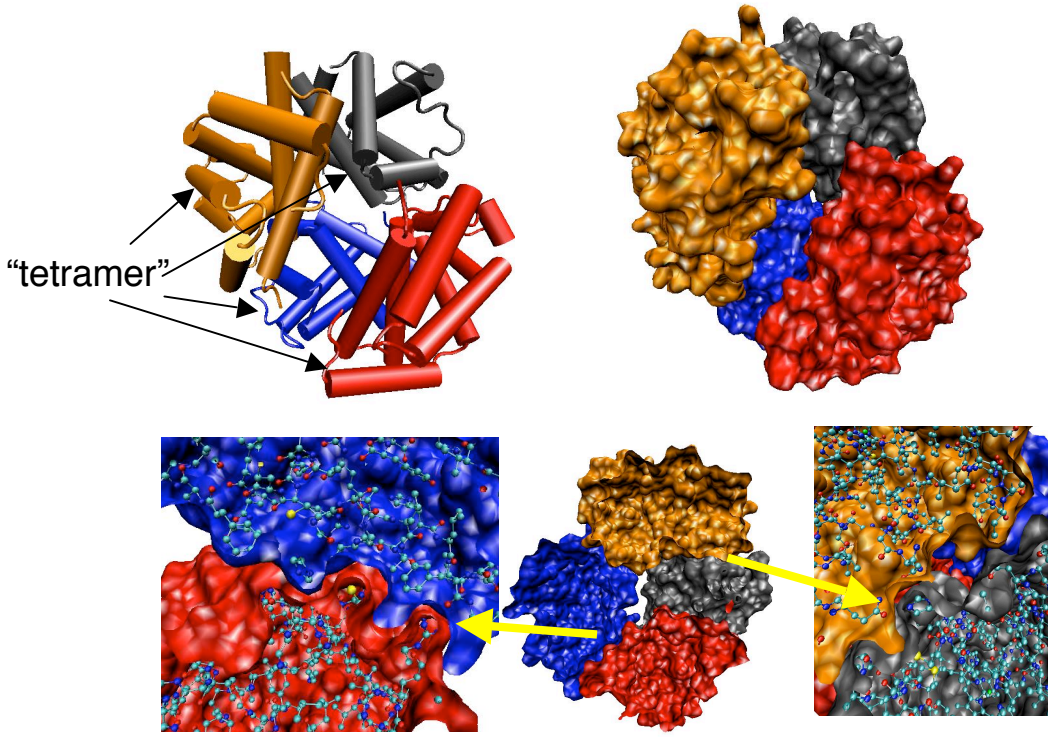


non-obligate permanent heterodimer:
thrombin-rodniin inhibitor

non-obligate transient heterotrimer:
bovine G protein

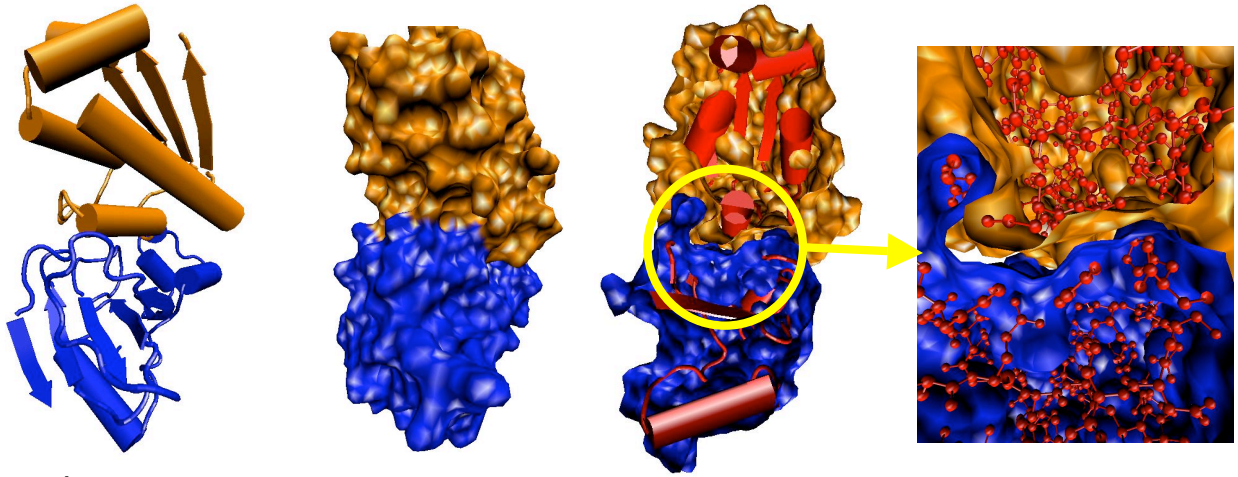


-initial glimpses of protein interaction surfaces were derived from structural studies of oligomeric proteins such as hemoglobin.



-cognate subunit interfaces look very much like non-cognate complex interfaces.

barstar

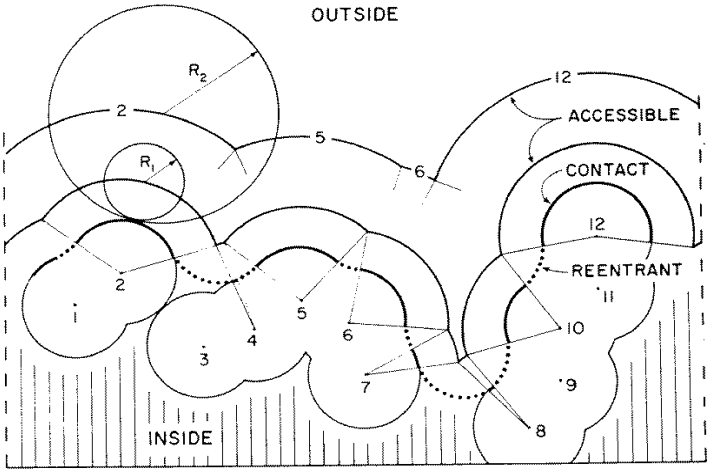


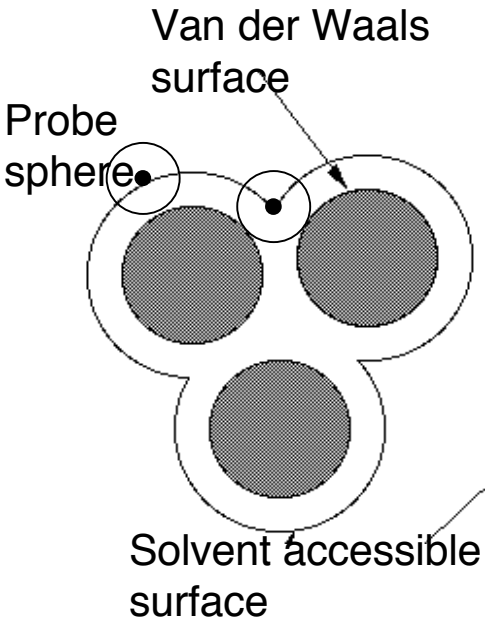
barnase

-chemists like Pauling, Anfinsen, Chothia and others predicted that protein-protein interfaces may look like a slice through the core of a single protein.

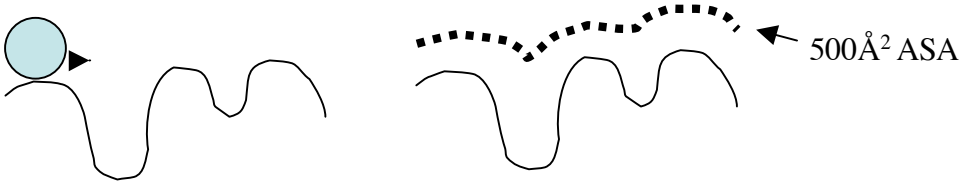
B) Surface Area (see http://connolly.best.vwh.net/netsci/msr1.html).

-An important term to understand when describing a protein interface.
-Idea was introduced by Lee & Richards (1971) to determine that hydrophobic amino acids lose more ASA than polar residues when a protein folds - thus folding is driven by hydrophobic effect.
-The accessible surface is traced out by the probe sphere center as it rolls over the protein. Usually the probe sphere is set to the VDW radius of water (1.7Å). *F. M. Richards, Ann. Rev. Biophys. Bioeng. 1977, 6:151*
-method is very useful analytical tool for protein interactions, but is very sensitive to probe radius thus discrepancies in literature.

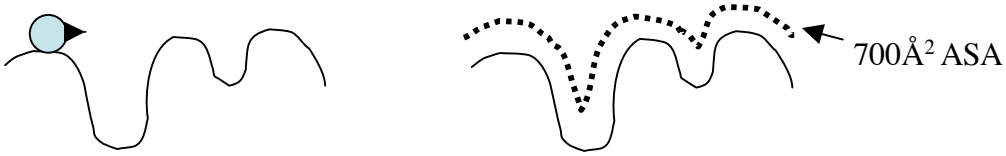




Effects of probe sphere radius:
-say probe of 1.7Å

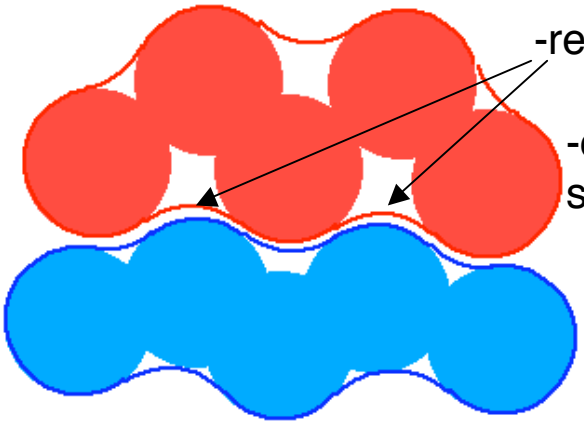


-now probe sphere of 1.4Å



-pictures of protein surfaces do not show ASA, but instead the "molecular surface."

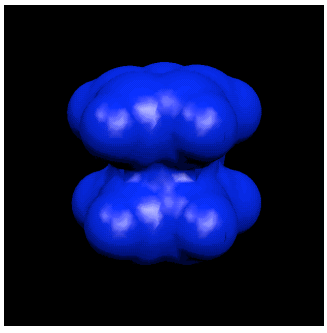
Molecular surface = reentrant surface + contact surface (Richards 1977):



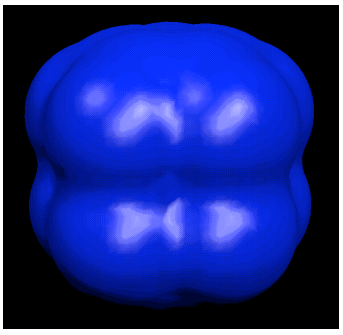
-is best for showing **shape complementarity**

Examples:

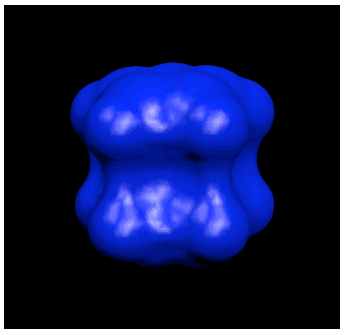
VDW



Solvent accessible surface area

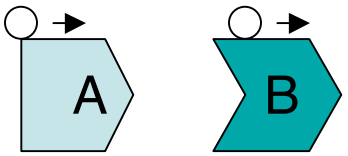


Molecular surface

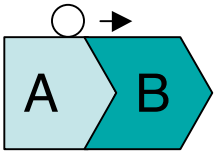


Calculate your own !
http://www.scripps.edu/pub/olson-web/people/sanner/html/msms_server.html

-in general the standard convention is
-to quantitate interface values in terms buried surface area (BSA).
-to calculate the BSA of an interface,
-subtract the ASA of each individual unliganded component from the ASA of the entire complex.



2000Å^2 2500Å^2



3500Å^2

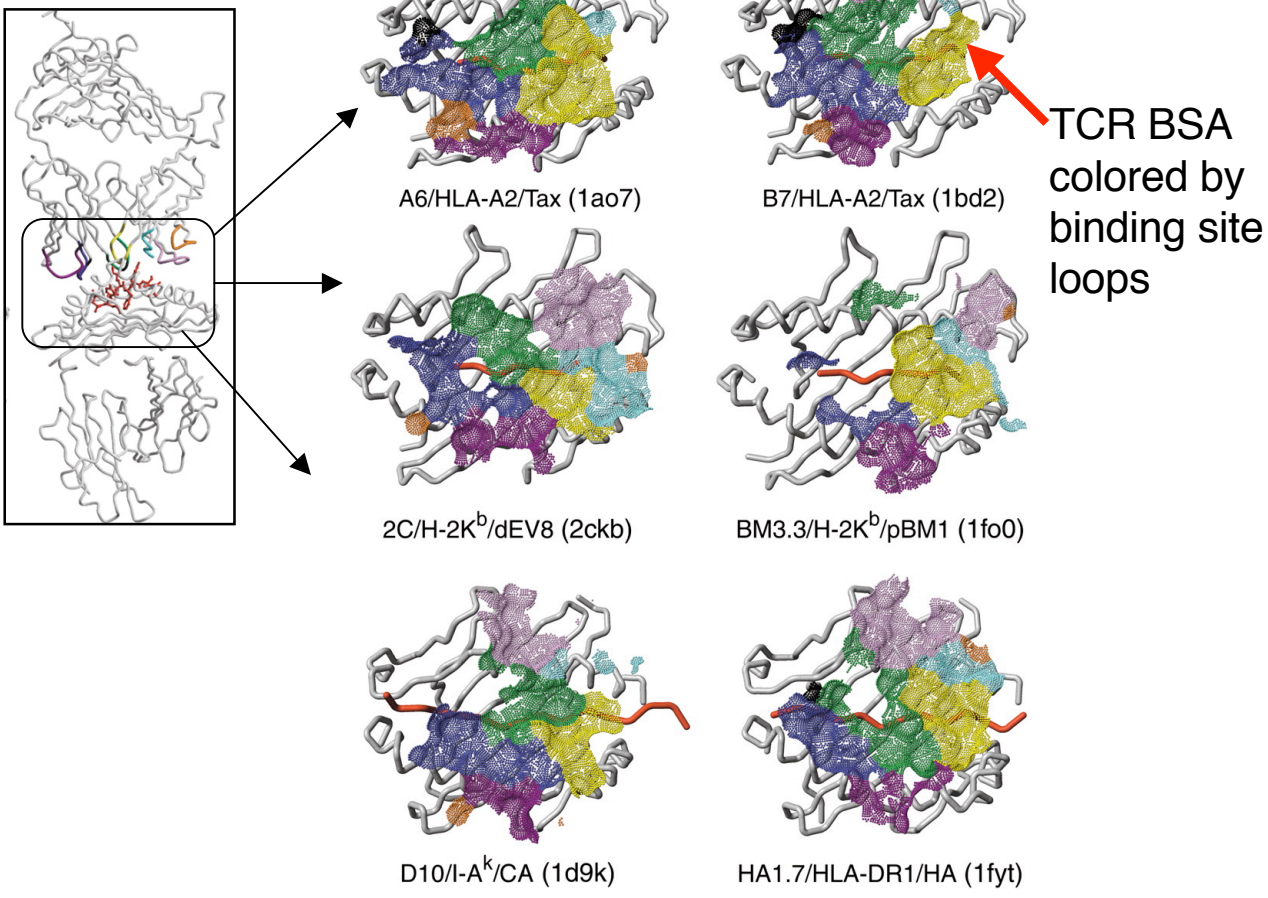
Total BSA = 4500 -3500 = 1000Å^2

Examples of the utility of BSA calculations:

Table 1. Crystal structures and analysis of T cell receptor/MHC complexes

TCR	2C	scBM3.3	B7	A6
MHC	H-2Kb	H-2Kb	HLA-A2	HLA-A2
Peptide	dEV8	pBM1	Tax	Tax
Res (Å)/Rf (%)	3.0/32.2	2.5/27.6	2.5/31.2	2.6/32.0
PDB ID/(Ref.)	2ckb	1fo0	1bd2	1ao7
BSA	1891	1239	1651	1801
TCR/MHC (Å2)	906/985	597/642	787/864	900/901
MHC/pep (%)	76/24	79/21	68/32	66/34
V (Å2)/(%)	490/54	221/37	526/67	577/64
CDR1/2/3 (%)	23/13/16	14/17/6	28/13/23	25/10/25
Vß (Å2)/(%)	417/46	376/63	261/33	321/36
CDR1/2/3/ (%)	16/17/10	10/14/39	0/11/22	2/0/33
Scc	0.41	0.61	0.64	0.64
HB/salt/vdW	7/1/80	8/3/83	7/1/98	15/4/104
Va	5/1/63	1/1/27	6/1/65	11/4/59
Vß	0/0/17	7/2/56	1/0/33	4/0/45
MHC	3/1/59	3/3/54	4/1/41	8/4/64
Peptide	2/0/21	5/0/29	3/0/57	7/0/40

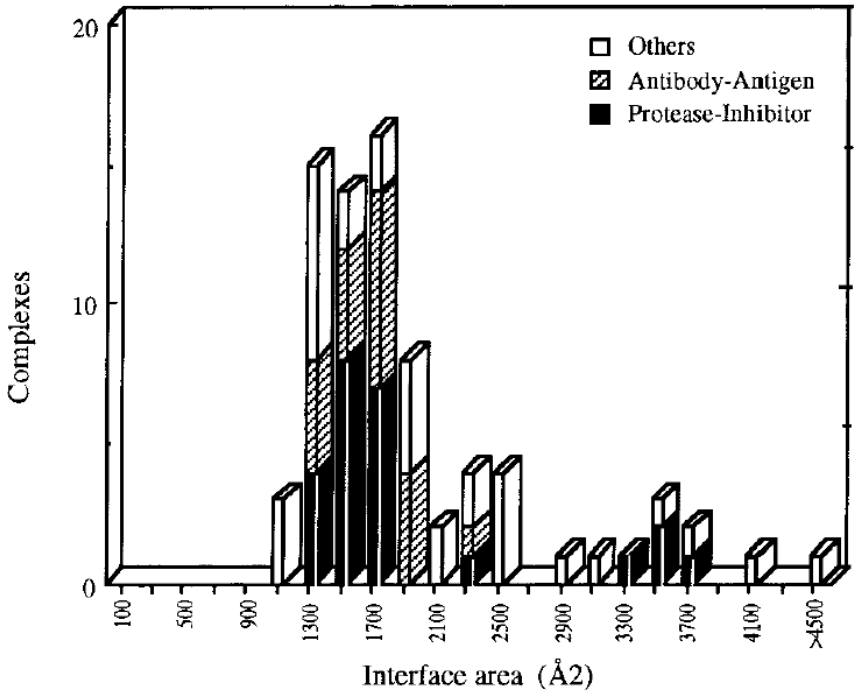
TCR/MHC “footprints”



-In general, BSA values for “real complexes” range from ~1000Å^2 to 2500Å^2.

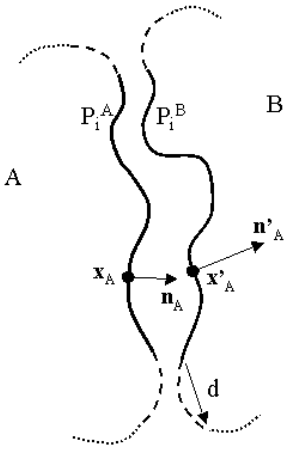
-Oligomer subunit interfaces, i.e. obligate complexes, have larger interfaces than non-obligate complexes. Why ?

pdbid	complex		BSA (Å^2)
1fc2	Protein A-Fc fragment	2.8	1300
1igc	Protein G-Fab MOPC21	2.6	1350
1ak4	Cyclophilin-HIV capsid	2.4	1170
1efn	Fyn SH3 domain-HIV Nef	2.5	1260
1atn	Actin-DNase I	2.8	1780
2btf	Actin-profilin	2.5	2090
1dkg	Grep E-DNA K	2.8	1980
1ebp	Erythropoietin receptor-peptide	2.8	1940
1hwg	HGH receptor-human growth hormone	2.5	4200
1seb	HLA DR1-enterotoxin B	2.7	1340
1tco	FKBP12-Calcineurin	2.5	2470
1ycs	p53-53BP2	2.2	1500
Protease-inhibitor		Mean	1530
		s.d.	170
Large protease complexes		Mean	3300
		s.d.	540
Antibody-antigen		Mean	1680
		s.d.	260
Enzyme complexes		Mean	2030
		s.d.	630
G-proteins, signal transduction		Mean	2500
		s.d.	1090
Miscellaneous		Mean	1870



C. Shape complementarity.

- protein-protein complexes generally exhibit good geometric complementarity.
- a simplistic but very important concept in protein-ligand intxns.
- difficult parameter to quantify.
- one measure is to use alignments of surface normals.



(Lawrence & Colman, 1993)

-comparison of naïve protein "docking" programs using either geometric (i.e. shape complementarity) or energetic (H-bonds, charges, VDW) complementarity revealed that shape complementarity alone can serve as a very accurate predictor of protein-ligand interfaces. (Nussinov, 1999).
-"goodness-of-fit" between a protein and ligand surfaces captures many, if not most, of the essential features of protein interactions.

For each point **x**A in PA we find its nearest neighbour **x**'A on PiB. Let **n**A be the outwardly-oriented surface normal at **x**A and **n**'A be the inwardly-oriented surface normal at **x**'A. Define the scalar function

SA->B(**x**A) = (**n**A.□n'A) exp[-w (l**x**A-**x**'Al)2]

on the surface PiA, where w is a scalar weight.

Likewise by considering all points **x**B on surface PiB we may define

SB->A(**x**B) = (**n**B.□n'B) exp[-w (l**x**B-**x**'Bl)2]

where **x**'B is the nearest point to **x**B on PA, **n**B the outwardly-oriented normal at **x**B and **n**'B the
inwardly-oriented normal at **x**'B.

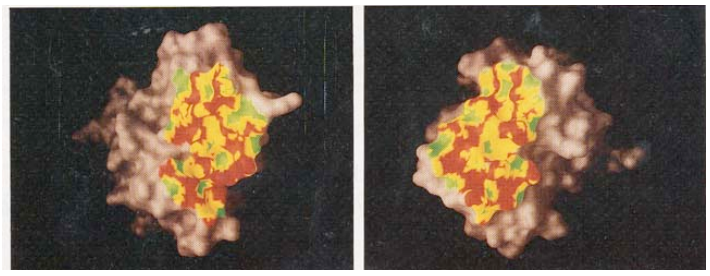
Sc is then defined as

Sc = ({SA->B}+{SB->A}) / 2

-Appears to be a general trend for obligate subunit interfaces to exhibit better complementarity than non-obligate complexes.

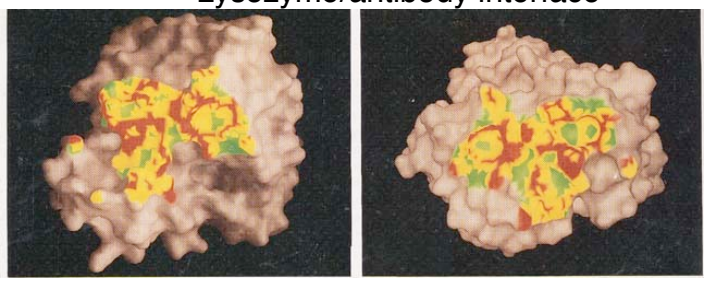
Protein/protein inhibitor interfaces:	SC
a-chymotrypsin/ovomucoid complex (1CHO)	.71
Subtilisin/eglin-C (2SEC)	.72
Trypsin/trypsin inhibitor (2PTC)	.76
Subtilisin novo/chymotrypsin inhibitor 2 complex (2SNI)	.72
Oligomeric interfaces:	
Human deoxy-Hgbn a/b subunit (2HHB)	.74
Phosphofructokinase a/b (2PFK)	.72
Insulin dimer (9INS)	.72
Neuraminidase subunit (1NCA)	.71
Phaseolin III	.70
Protein/Protein:	
Lysozyme/D1.3 Fab (1FDL)	.66
Lysozyme/HYHEL5 (2HFL)	.65
Lysozyme /HYHEL10 (3HFM)	.68
NC41/FAB (1NCA)	.66
Barnase/Barstar (1B27)	.81
TCR/MHC (2CKB)	.47
Chemokine/receptor (1MLO)	.62

Neuraminidase subunit interface

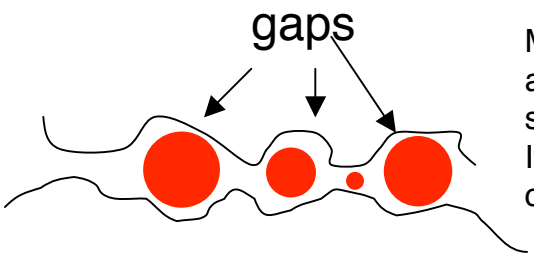


(best SC in red)

Lysozyme/antibody interface

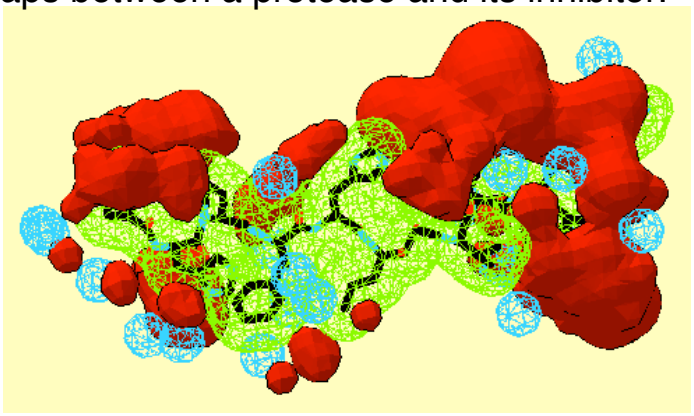


-Others define geometric complementarity in terms of gap volumes.
-Quantify the volumes of “gaps” or “clefts” within an interface.

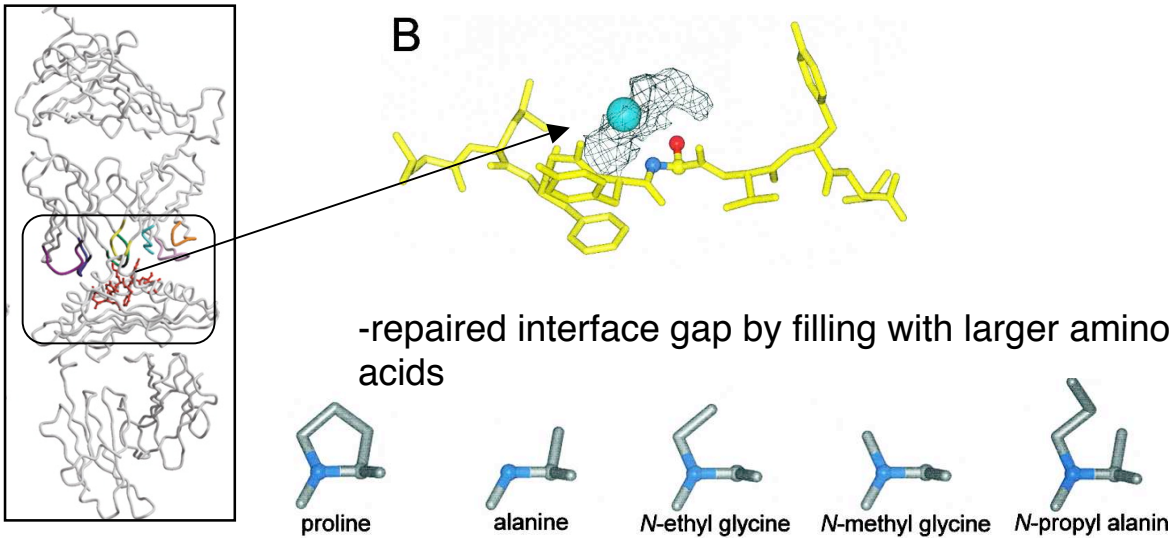


Method: 5Å sphere is placed halfway between atoms on either side of the interface. Checks to see if any neighboring atoms intersect the sphere. If so, the sphere radius is reduced until there are no clashes, and sphere size is recorded.

Example: gaps between a protease and its inhibitor.



“Useful” Example: correction of a packing defect in a TCR/MHC interface leads to conversion of an antagonist into a potent agonist (Baker & Wiley, 2000).

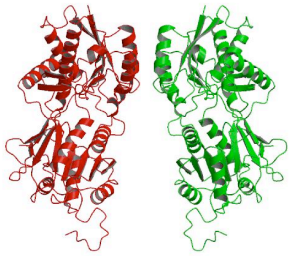


Laskowski R A (1995). SURFNET: A program for visualizing molecular surfaces, cavities and intermolecular interactions. *J. Mol. Graph.*, **13**, 323-330.

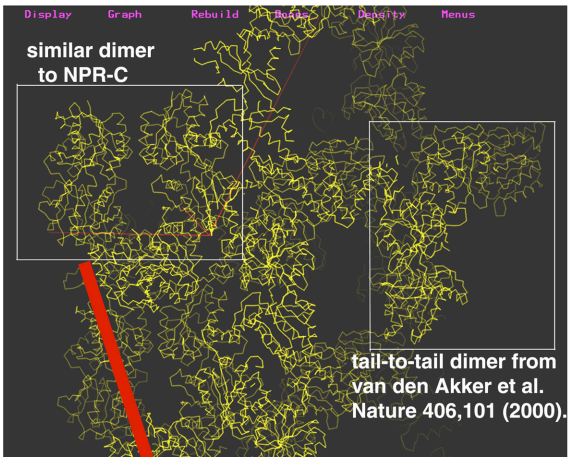
Surface area and complementarity can reveal biologically relevant interfaces:

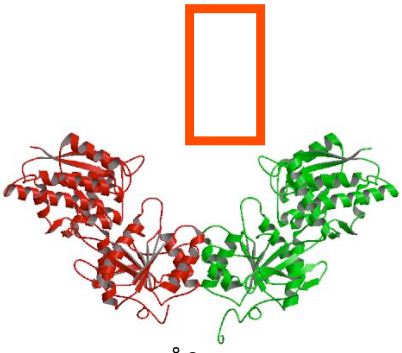
Example 1: Multiple dimers in receptor crystal lattice. Initially, a dimer interface with Small BSA and poor SC was chosen as the relevant dimer. Simple check of these values for other dimer in crystal would have shown alternative dimer is more plausible.

NPR-A crystal packing (PDBID1DP4)



2500Å^2 BSA, .75 Sc
(He et al, 2001)

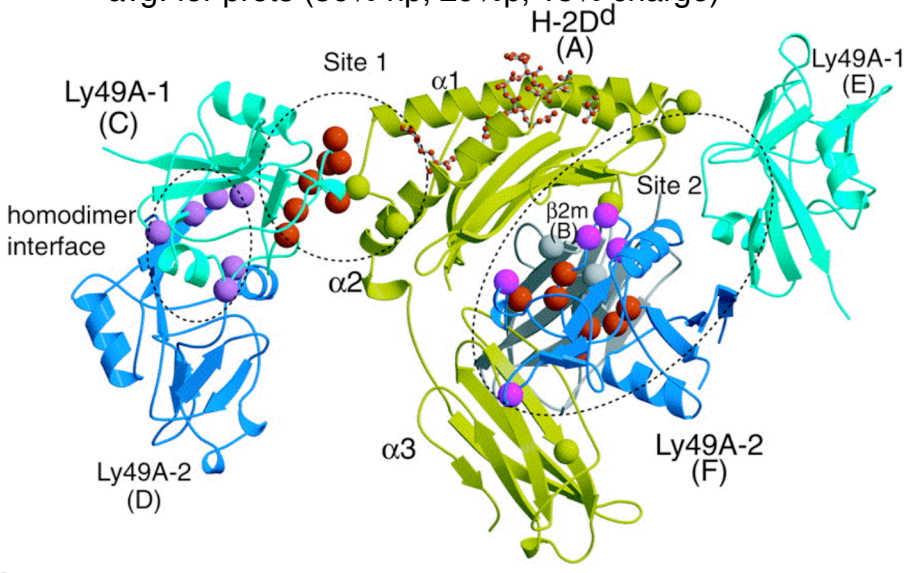




800Å^2 BSA, .6 Sc

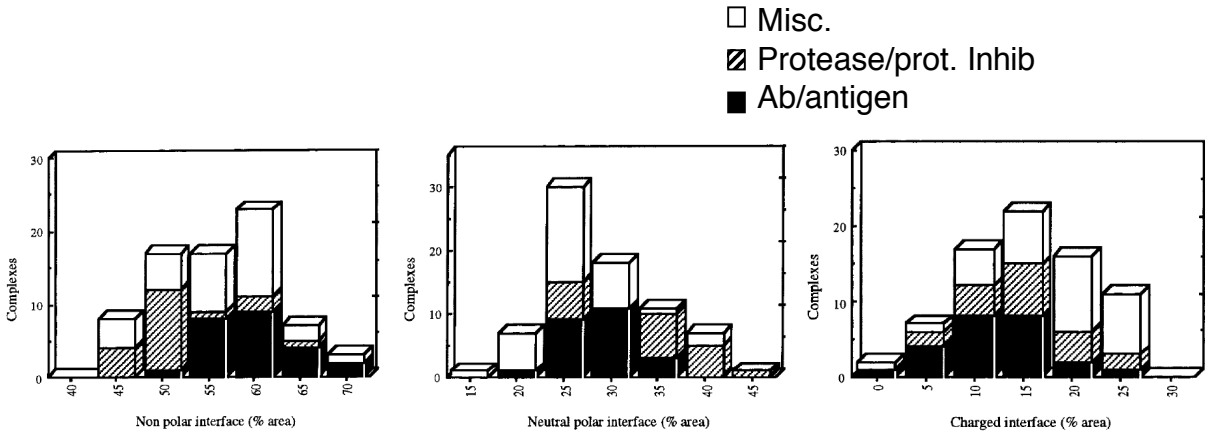
Example 2: Complex of MHC with natural killer receptor. In crystal, two receptors bound to MHC ! We know it is 1:1, so which is the right interface ? (Li et al., 2000)

Site 1: 994Å^2 (35% non-polar, 29% neutral polar, 43% charge) , Sc=.72
avg. for prots (56% np, 29%p, 15% charge)



Site 2 : 3300A^2 (primarily polar) , Sc=.54

D. Chemical complementarity (reviewed in LoConte, 1999; Jones, 1996).



-hydrophobics dominate.

-on *average* ~1 H-bond per 100Å^2

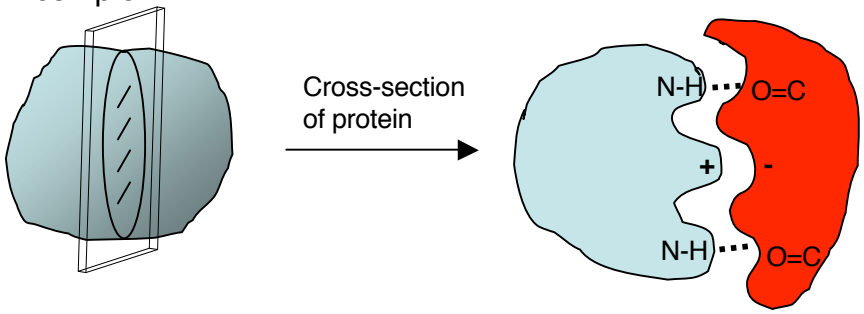
-rarest, most difficult to model energetics, why ?

Important concept: why do proteins associate ?

-Richards, Janin, Chothia, etc. made an important realization, that the interface between proteins looks like the interior of a protein (i.e. close packed, excellent complementarity).

-How does each interaction contribute to the free energy of association ? Key answer is that when protein-protein bonds are broken, the interface surfaces are not placed in a vacuum, but are covered by solvent (ions and water).

-Most of the bonds that are formed across the interface are replaced by water when the proteins are not in complex.



-the energetic consequence of this argument is that ionic bonds, H-bonds, and VDW forces make little NET enthalpic contribution to the free energy of binding since bonds are not lost upon dissociation but are **replaced** by water.

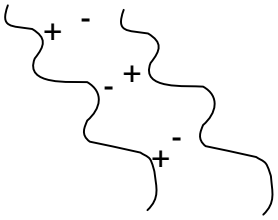
-however, the preference for complex formation may be derived from the entropic advantage of numerous weak interactions on a fixed surface, and superior bond stereochemistry and geometry within the protein interface versus randomly oriented water molecules.

-charge, H-bonds and VDW play primary role in determining specificity through requirements for precise chemical and steric complementarity

-chemical complementarity is composed of three features:

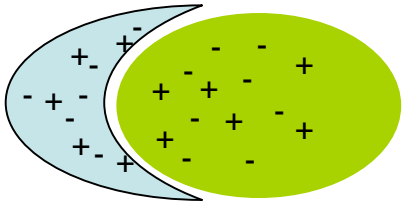
1- Charged interactions.

-Salt bridges (<4.0Å apart) can contribute significantly to the energetics of association.
-charges must be complemented by either partner protein or solvent since they are worth 5-20 kcal.mol, burying charge that is not complemented is very expensive.
-"charge complementarity" does not occur with any statistical significance in protein interfaces. That is, charge complementarity defined in a nearest neighbor sense where a charged atom is complemented by an opposing charged atom across the interface.
e.g.



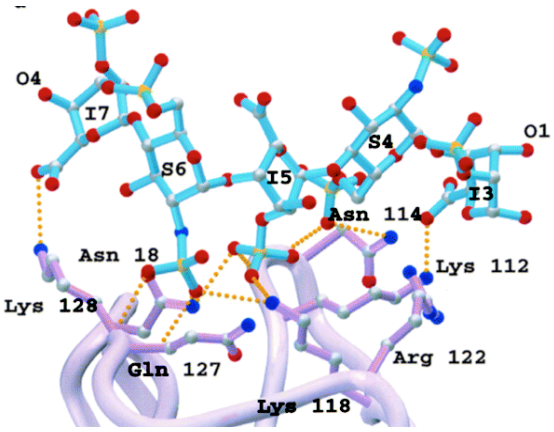
-this simple-minded approach does not consider the effects of long-range charges.

-however, interfaces do show clear "electrostatic complementarity" where the overall surface charge of the buried area is calculated as an electrostatic potential.
-development of a "continuum" electrostatics model for proteins through solving the Poisson-Boltzman equation for the protein-solvent system (such as that implemented in DelPhi - Gilson & Honig, 1988:Nichols & Honig, 1991) .

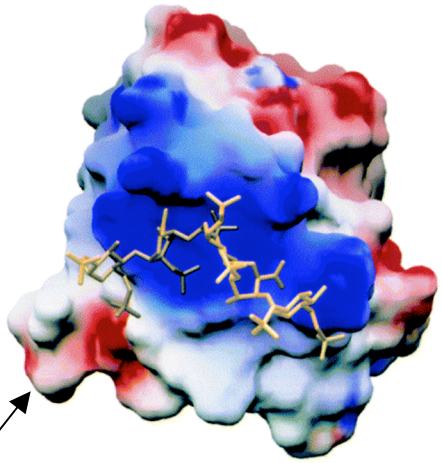


Example: fibroblast growth factor complex with heparin (DiGabrielle et al. 1998)
-dramatic basic patch on FGF even though only a few charged basic residues.

Interatomic contacts



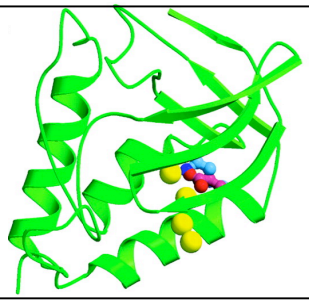
"GRASP" surface



these "hard sphere" representations map the EP onto a molecular surface. Remember that the EP formally extends to infinity so these are just very qualitative pictures of the EP at an arbitrary point in space and do not convey the power of long-range interactions.

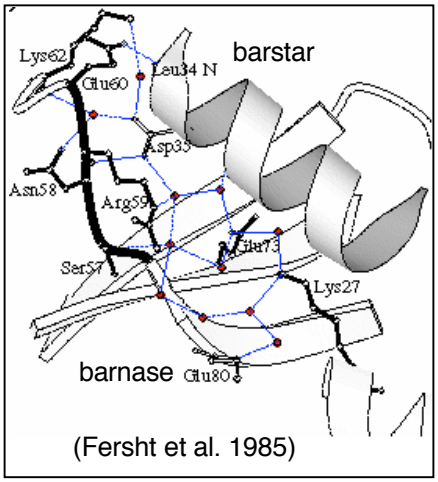
- While elec. surface potential can be calculated, the contribution of charges to the energetics of association (i.e. “solvation free energy”) is very difficult to model accurately.
-Enormous variability for contributions of dieletric constants (2 inside to 80 outside), and hydration.
Choice of dielectric constant profoundly affects continuum potential calculations. For example, the assumption that protein interior is low DE greatly exaggerates the magnitude of electrostatic effects.

Example: Glu buried in hydrophobic core of Staph. Nuclease suggests that interior dielectric is significantly higher than we think (Dwyer et al.,2000). However, may only reflect microscopic accommodation to Glu with no bearing on the dielectic constant.



2- Hydrogen bonds.

-polar groups must be satisfied within interface.
-H-bond donors and acceptors must find complement, otherwise will lose between 0.5 and 6 kcal/mol.
-the energetic content of the H-bonds is dependent on the geometry and distance of the bond.
-is very difficult to predict energetic content of H-bond.
-Water is a very effective mediator of specific protein interactions.



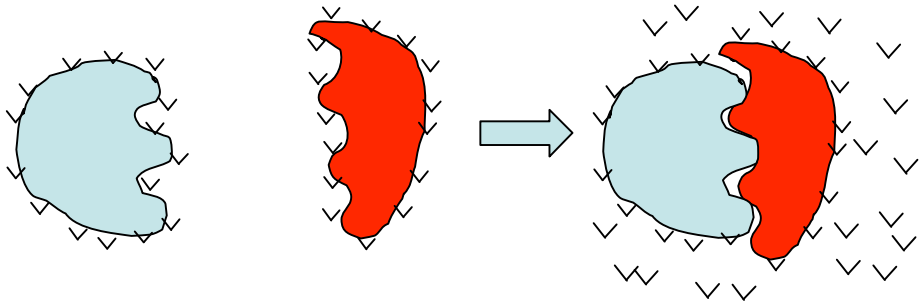
(Fersht et al. 1985)

3- van der Waals - “steric” complementarity.

-Protein interfaces are covered with water molecules making VDW contacts with all exposed atoms on the surface.
-Even though VDW are worth only ~1kcal/mol, there are many of these interactions.
- VDW contacts between interface and water must be replaced by protein-protein contacts, necessitating a very tight packing in the interface since even a separation of only 1Å will eliminate the VDW energy.
-packing densities within protein interfaces approaches that of protein cores.
-VDW forces dominate the total BSA of most interfaces.

4- Hydrophobic interactions.

-as for protein folding, is the major determinant of protein-protein interactions.



-"frozen" waters would much rather interact with other waters than make vdw non-polar with protein atoms.

-massive gain in entropy of the system drives the two interfaces together, accompanied by desolvation

-the magnitude of the hydrophobic effect can be estimated through proportionality constants relating the area of protein surface that is removed from contact with water to the free energy of the interaction.

-model compound data measured by partitioning amino acids between water and non-polar solvents give a value of ~.025kcal/mol for each 1Å^2 of hydrophobic surface removed from water.

-e.g. an interface of 1000-1500Å^2 (insulin dimer, hemoglobin subunit interface, trypsin-BPTI) should have overall favorable free energy of about 30-40kcal/mol. In fact, these estimates greatly overestimate actual free energy.

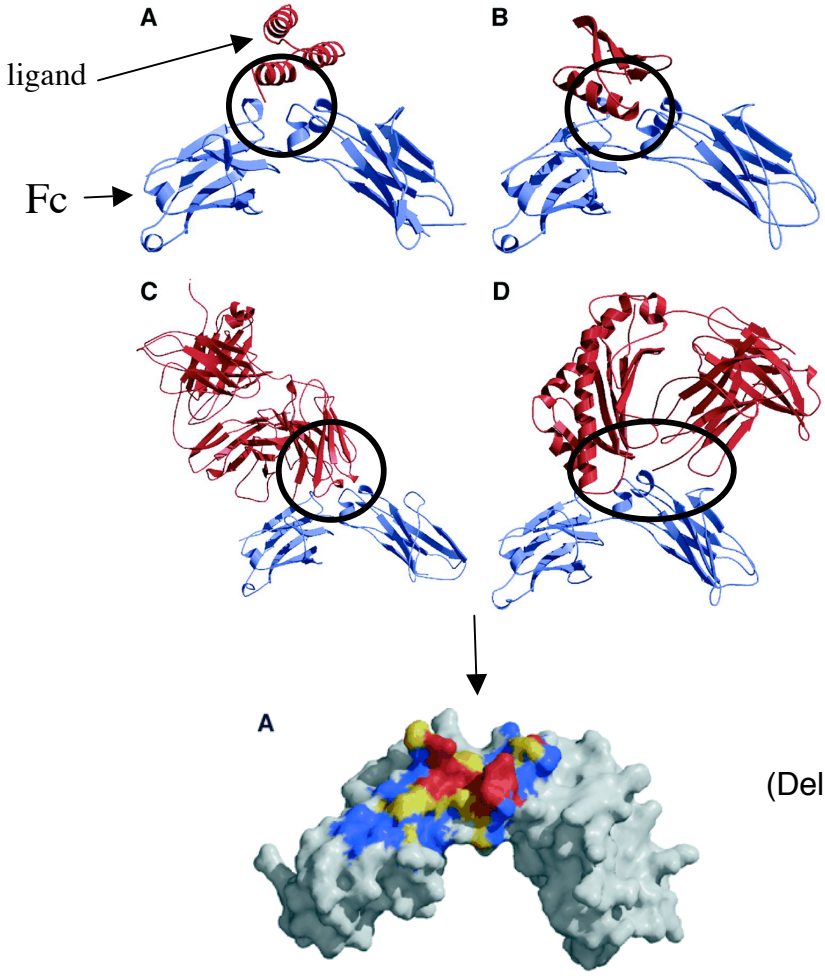
- how would one experimentally measure hydrophobic effect ?

What is a “protein binding site ?”

E. Towards comprehensive models of protein binding sites.

-“protein “binding sites” cannot be described with certainty by a single, or even multiple discrete parameters.
- binding sites are probably unique relative to other areas of protein.
- can we inspect atomic coordinates of a protein structure and predict the binding site ? (what makes a binding site unique ?)
-advent of human genome sequence > structural genomics has underscored the importance of binding site prediction on a protein structure of unknown function.
-a number of methods, based on somewhat empirical parameters, have been developed to predict a binding site on a protein surface. “Patch analysis”

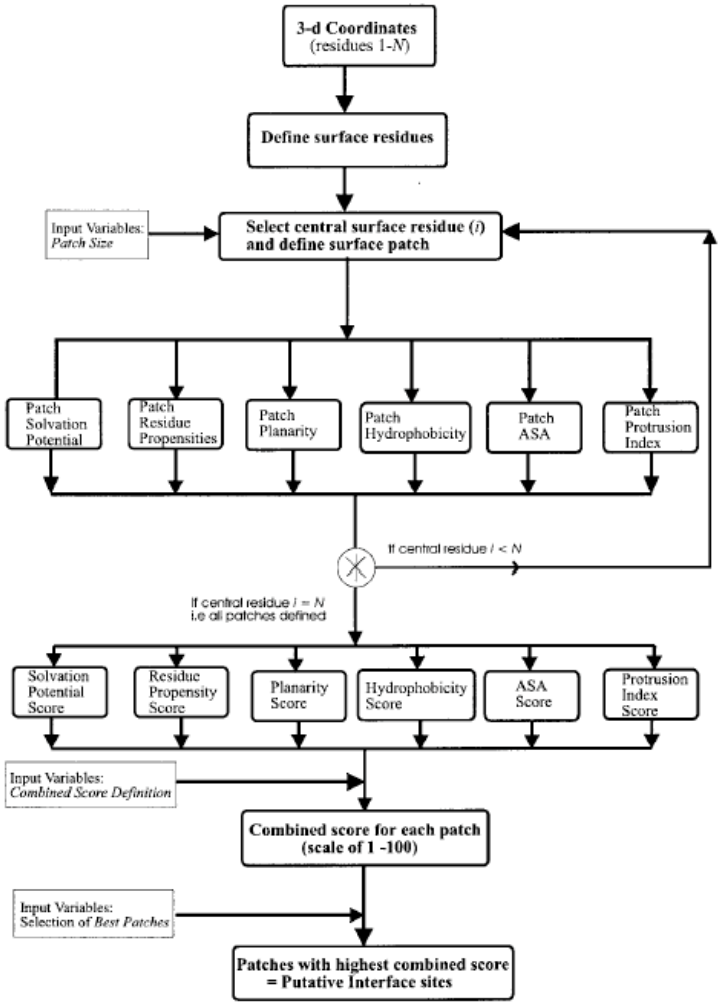
Example: Human Fc receptor binds to four different proteins using the same binding site.
-what features endow this protein with such favorable features for protein-protein interactions ?



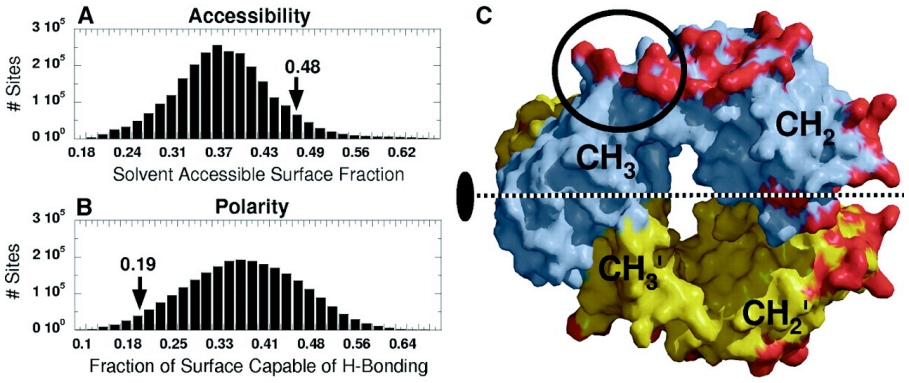
(Delano et al., 2000)

Can we computationally predict protein binding sites ?"

Example: Patch strategy calculates a series of geometric and chemical characteristics of A region of defined radius for each amino acid on the protein and compares them to statistics derived from the database of known protein-protein interfaces (Jones & Thornton, 1997 & many related programs by others):

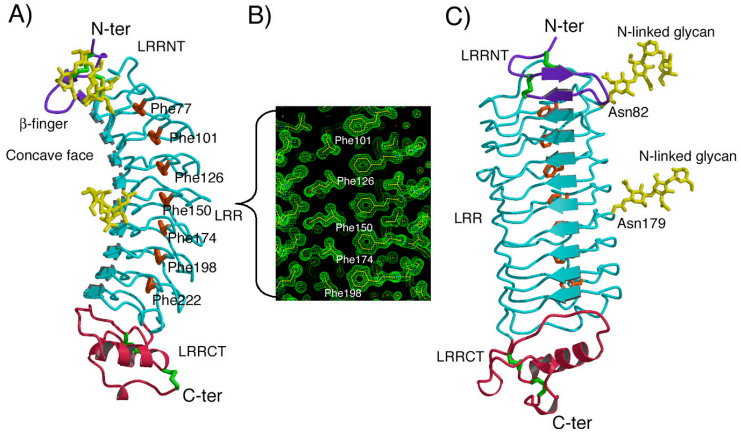


patch analysis predicts binding site (more accesible, less polar)

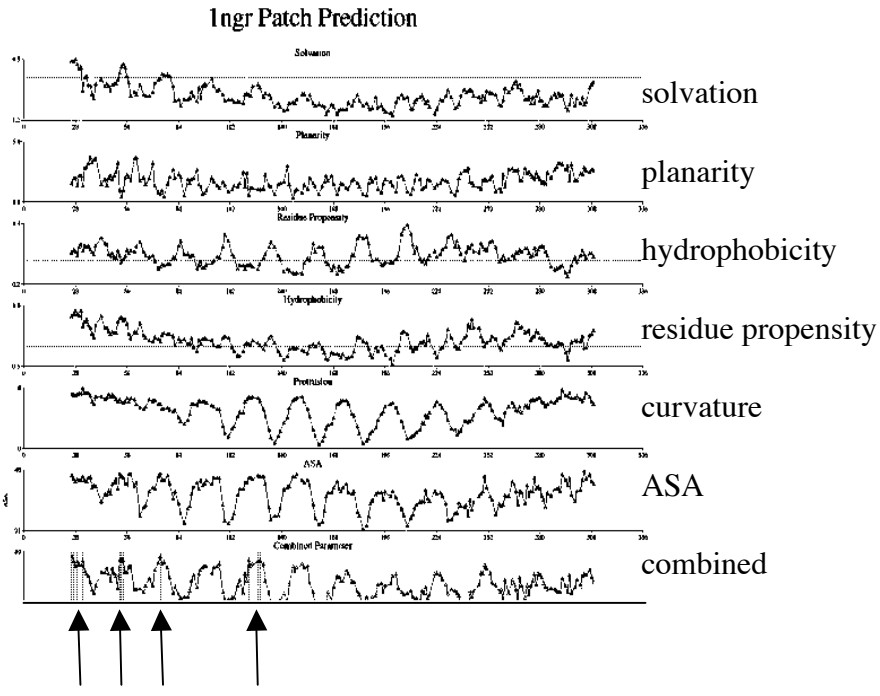


Do binding site prediction algorithms work ?

Test case: Nogo receptor. An important receptor in axonal guidance. Three known ligands convergent on a single area on the protein. X-ray structue of uncomplexed Receptor determined to 1.5Å resolution. Two different prediction programs attempted to identify binding site(s).



Thornton method:



solvation

planarity

hydrophobicity

residue propensity

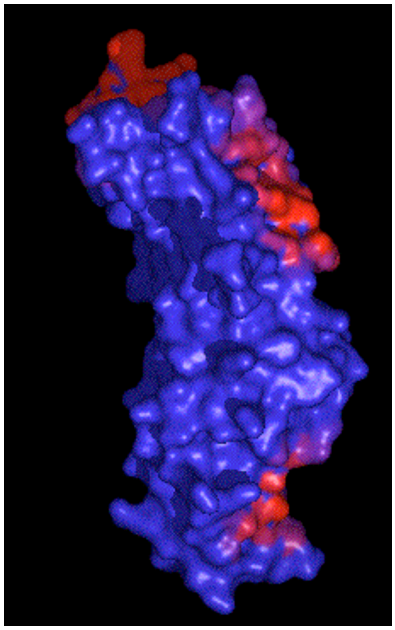
curvature

ASA

combined

-N-terminal regions and back.

Delano method:



-predicts top and back of structure.

-neither program correctly assigns binding site. Functional studies have located the ligand binding site to the "belly" of the leucine-riich repeat.

Can we describe the energetics of protein interactions from structure ?

II. "Structural Energetics" (Papers by E. Freire, J. Janin, K. Murphy, Jen-Jasobsen).

- from structure, we can say something about thermodynamics, and vice versa.

$$\Delta G = -RT\ln K$$

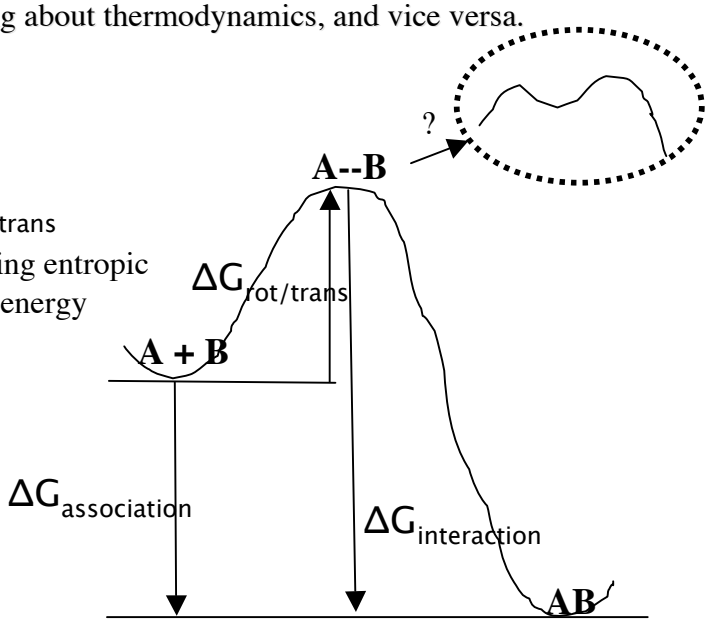
$$\Delta G_{association} = \Delta G_{interaction} + \Delta G_{rot/trans}$$

observed binding free energy

intrinsic binding free energy

opposing entropic free energy

controversial, estimates range from 7 to 25 kcal/mol



example of values:

-for a protein-protein association of $K_D=10^{-9}M$ ($K_A=10^{9}M^{-1}$)

$$\Delta G_{association} = 600 \ln (10^9) = -13.8 kcal/mol$$

$$\Delta G_{association} = \Delta G_{interaction} + \Delta G_{rot/trans} = -13.8 kcal/mol$$

-using 10kcal/mol of unfavorable association entropy (i.e positive value).

$$\Delta G_{association} = \Delta G_{interaction} + 10 kcal/mol = -13.8 kcal/mol$$

-hence,

$$\Delta G_{interaction} + 10 kcal/mol = -13.8 kcal/mol$$

$$\Delta G_{interaction} = -23.8 kcal/mol$$

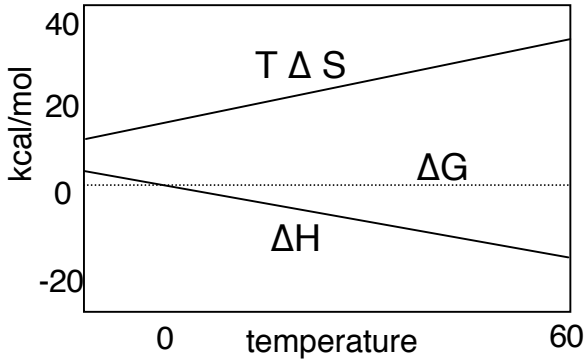
-intrinsic free energy must be very high in order to compensate for the very unfavorable "cratic entropy" term, which is almost as large as the net free energy of association !!

- what is $\Delta G_{interaction}$?

-is composed of both enthalpic terms (VDW bonds, H-bonds, charges) and entropic terms from hydrophobic effect.

$\Delta G = \Delta H(T) - T\,\Delta\, S(T)$ $\Delta Cp = d(\Delta H)/dT = T(d(\Delta S))/dT$

"**enthalpy-entropy compensation**" - a mutation in a protein interface may not reveal itself in overall free energy, rather the interaction energy may redistribute itself between entropy and enthalpy. Characteristic of systems with multiple weak interactions.



-one never speaks of an "enthalpy-driven" or "entropy-driven" process without specifiying the temperature. (see Jen-Jacobsen paper for excellent Discussion).

-the temperature dependence of the ΔH, called heat capacity (Cp), reflects the exposure of non-polar surface to solvent. A large positive Cp is an indication that the hydrophobic residues exposed. Large negative Cp of an interaction means that hydrophobic residues are being shielded from solvent upon complex formation. Most protein intxns exhibit negative Cp.
-the magnitude of Cp depends on the number of ways of distributing heat into the system, and is thus related to entropy. For instance, to bring about a 1 degree rise in T, a system with few degrees of freedom will not require much energy. However, a system capable of undergoing conformational change will require more energy to bring about the same rise in T, due to many ways of distributing the input energy.

-in fact, since Cp is proportional to the exposure of surface, Cp has been "parameterized" into proportionality constants that allow one to calculate Cp from structural data (P. Privalov).

$$\Delta Cp = \Delta Cp_{apolar} + \Delta Cp_{polar} \quad \text{(units cal } K^{-1}\ mol^{-1})$$

$$\Delta Cp = (0.45 cal/K/Å^2)\Delta ASA_{apolar} + (-.26 cal/K/Å^2)\Delta ASA_{polar}$$

-Protein folding/unfolding data have shown that enthalpy and entropy also scale with exposure/burial or apolar/polar SA.
-Cp now allows calculation of ΔH based on another set of atomic solvation parameters (Eisenberg & Maclachlan, 1986).
-enthalpy is calculated with reference to the average midpoint temperature for protein denaturation (60°C):

$$\Delta H(60^{o}) = \square\square\square\Delta ASA_{apolar} + \square\square\square\Delta ASA_{polar}$$

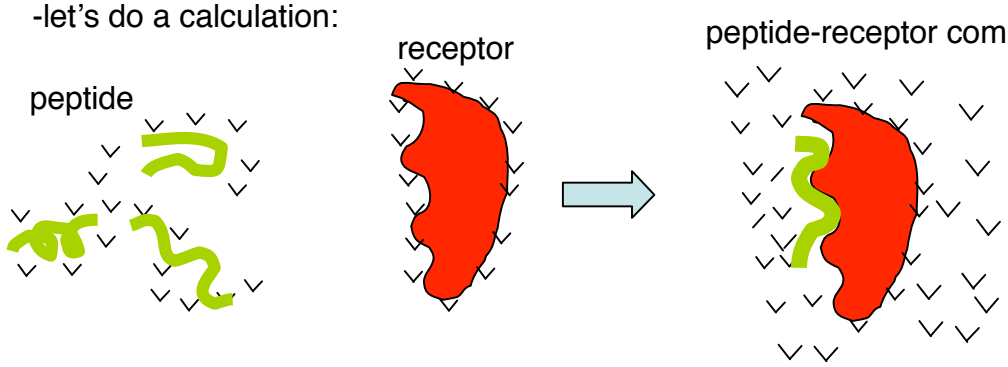
$$\Delta H(T) = \Delta H(60^{o}) + (\Delta Cp_{apolar} + \Delta Cp_{polar})(T-T^{*})$$

-The entropy of solvation can be written in terms of heat capacity if the temps where the apolar and polar contributions to solvation entropy are zero are used as reference.

$$\Delta S(T) = \Delta Cp_{apolar}\ \ln(T/T^{*}_{apolar}) + \Delta Cp_{polar})\ln(T/T^{*}_{polar})$$

-the implication of this is that overall free energy of binding can be calculated if we have atomic coordinates of the protein-protein interface based on the observation that free energies of association appear to rely mainly on burial of apolar and polar surface area.

-let's do a calculation:



upon complex formation, $\Delta ASA_{apolar} = 993 Å^2$

upon complex formation, $\Delta ASA_{polar} = 745 Å^2$

$\Delta Cp = -250$ cal K^{-1} mol^{-1}

$\Delta H = -8.4$ kcal/mol

$\Delta S = 8$ cal K^{-1} mol^{-1}

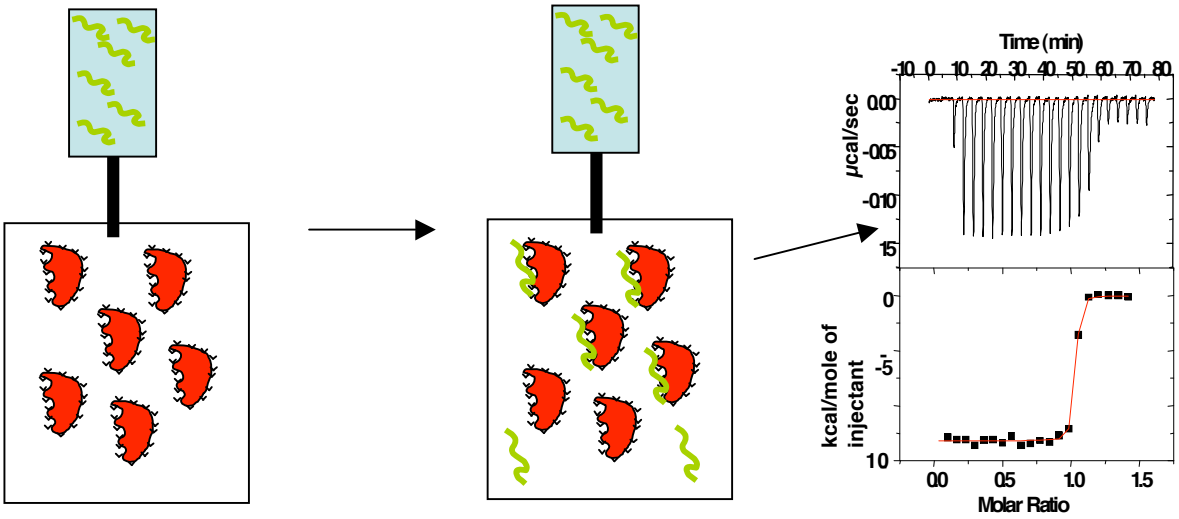
entropically favorable !

$\Delta G = -11$ kcal/mol

is it correct ?

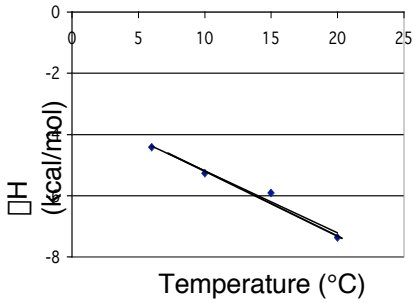
-let's check these predictions with experimental measurements:

Isothermal Titration Calorimetry allows the direct measurement of the heat of an interaction.
-ligand is titrated into a receptor in a cell, and a very sensitive thermo-couple measures the heat absorbed or evolved.
-the energy of the interaction is plotted against time, and the area under the curve represents the enthalpy of the interaction. Titrating to saturation yields an overall free energy.
- carrying out the experiment at multiple temperatures will then provide Cp, and entropy can be calculated using the relationship $\Delta G = \Delta H(T) - T \Delta S(T)$.



measured values:

ΔG =-12 kcal/mol
ΔH =-9kcal/mol
ΔS = 6.9cal/K/mol
ΔCp =-240 cal/K



-in this case, the experimental values match the predicted very well. why ?
-in most cases, the predicted free energy of association is massively overestimated.
-the reason is a basic misconception about the **energetic landscape** of protein interfaces.

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