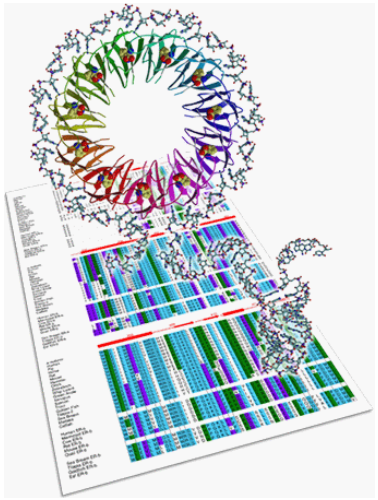
Escuela Complutense de Verano
Especialista en Bioinformática



Interacciones entre proteínas y pequeños ligandos (I)

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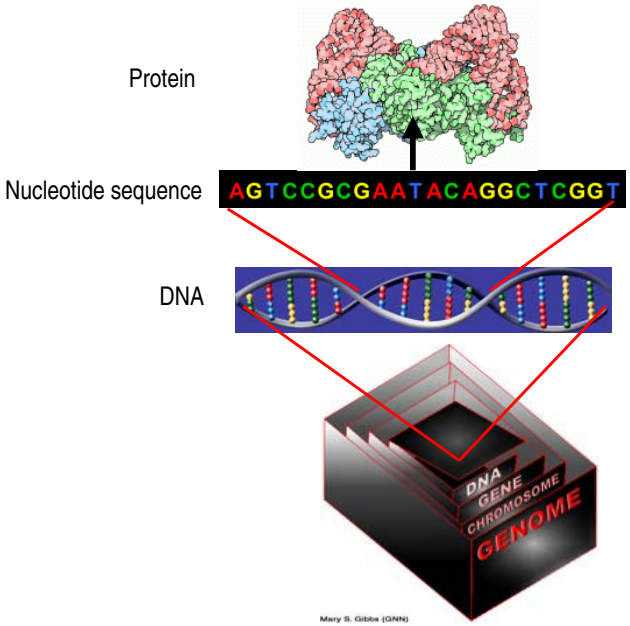
Interacciones entre proteínas y pequeños ligandos

1. Funciones de las proteínas y movimientos asociados.
2. Concepto de ligando y sitio de unión. Ejemplos.
3. Bases de datos estructurales y programas asociados.
4. Caracterización estructural de moléculas pequeñas y sus complejos con proteínas.
5. Acoplamiento ligando-receptor ("docking"): algoritmos y programas.
6. Cribado virtual.
7. Relaciones estructura-actividad: QSAR y 3D-QSAR.
8. Diseño de nuevos ligandos.

Gene expression = Protein production



How Proteins Work

Proteins recognize and reversibly bind to other molecules: *cofactors, substrates, inhibitors*… Also *ions* and other *proteins*.

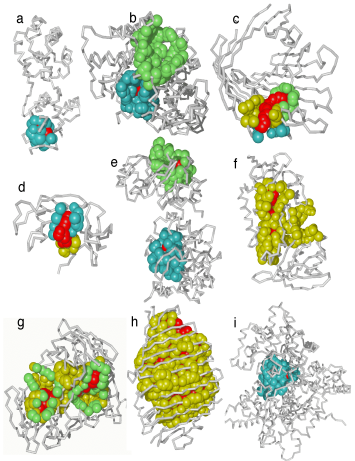
The bound molecule is called a **ligand**.

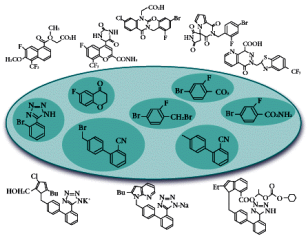
The region of a protein that associates with substrates and products is called the **active site**.

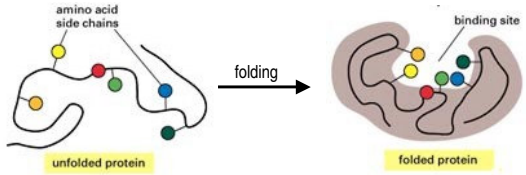
The region of a protein that associates with activator or inhibitor molecules is called an **allosteric site**.

Proteins can have > 1 binding site for different ligands

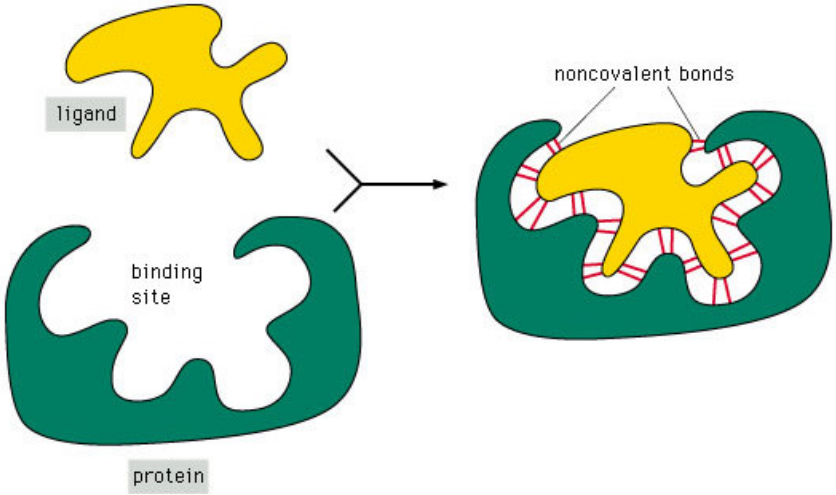
Proteins fold in such a way that they create specific sites that are the right *size*, *shape*, and *polarity* for their ligands.



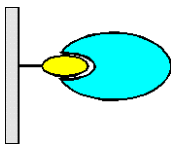




Ligand binding is highly selective

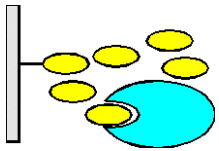


Affinity chromatography is a powerful purification method: the protein binds specifically to a **ligand**



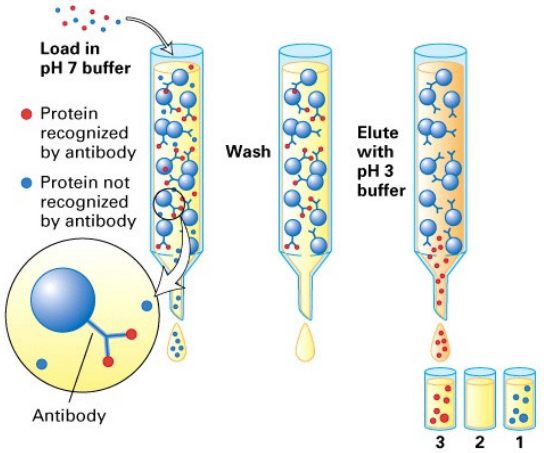
Ligand is covalently bound to the column

Protein specifically binds to a ligand for which it has a high affinity.

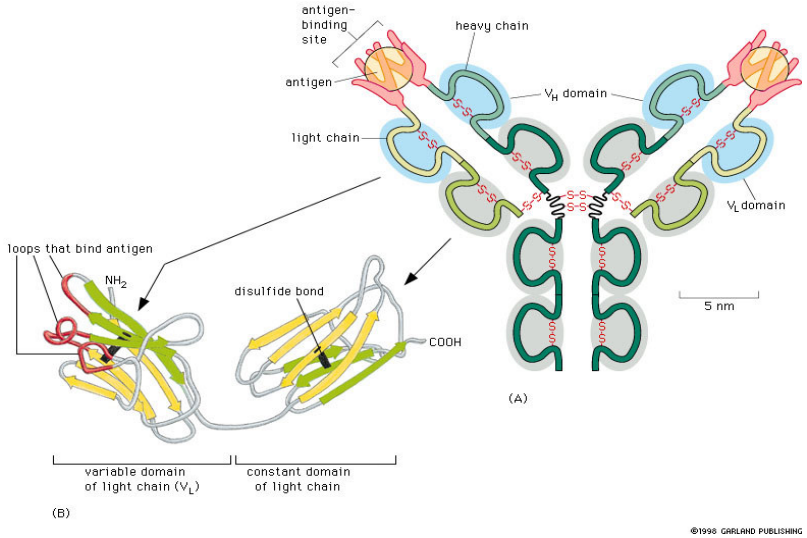


Elution of protein with unbound ligand

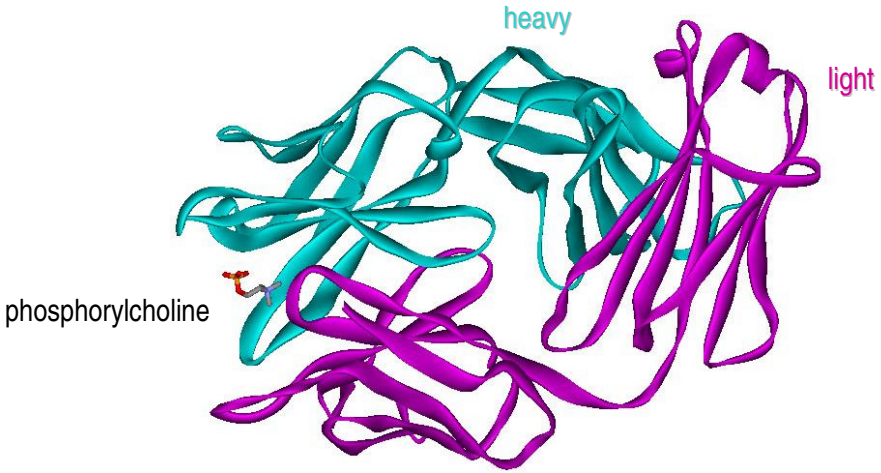
Separation of proteins by specific binding to another molecule: affinity chromatography



Antibodies selectively bind to antigens



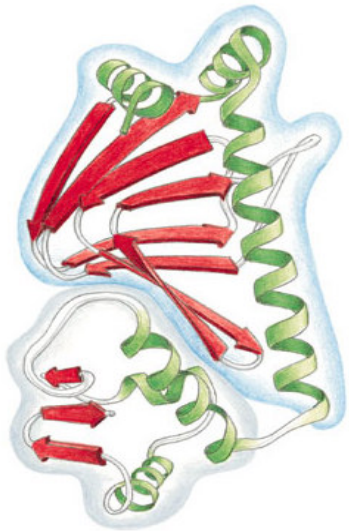
Immunoglobulin McPC603 Fab-Phosphocholine Complex (2mcp.pdb)



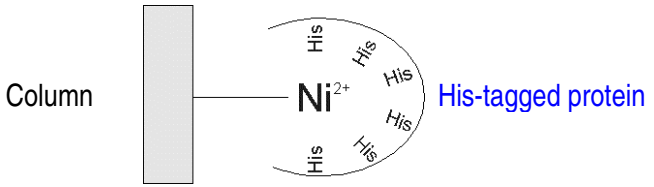
Protein Domains

Different parts of a polypeptide chain can fold independently to form a stable structure called a domain.

The different domains of a protein often have different functions such as the DNA binding domain (small) and the cyclic AMP binding domain of the CAP protein shown.



Smallest ligand binding domain: His-His-His-His-His-His His-tag



Advantages:

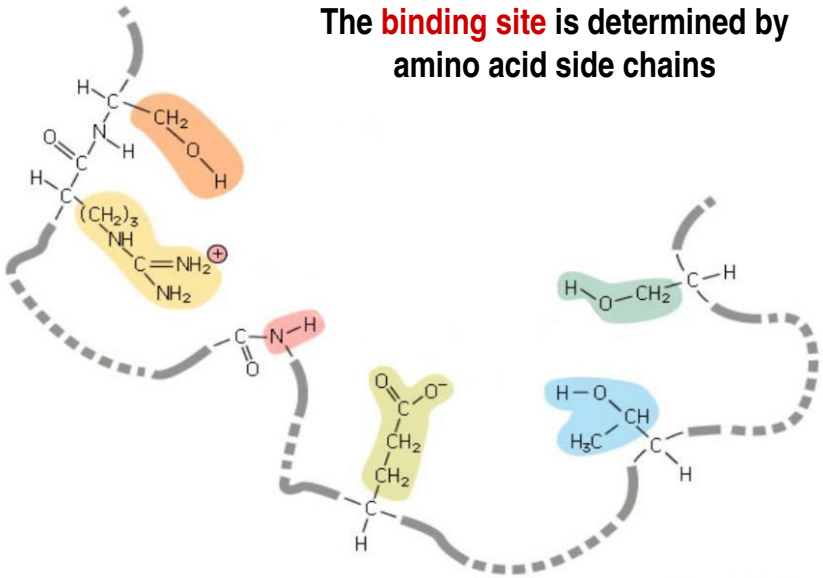
His-tags usually do not influence activity of protein, no need for removal

Allows purification in large quantities

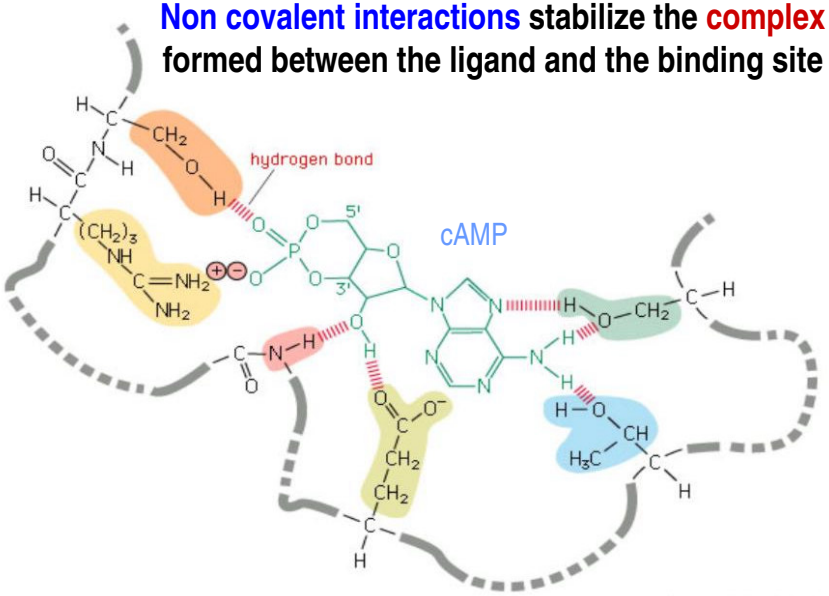
Simple to construct

Antibodies against the His-tag are available: detection of protein without need for specific antibodies

The **binding site** is determined by amino acid side chains



Non covalent interactions stabilize the **complex** formed between the ligand and the binding site



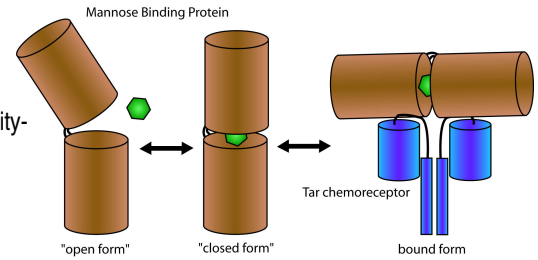
Proteins are:

Function	Example
Enzymes	DNA polymerase
Structural	collagen
Transporters	hemoglobin
Motors	myosin
Storage molecules	casein
Signalling molecules	insulin
Receptor molecules	rhodopsin
Regulatory molecules	lactose repressor
Speciality molecules	antifreeze
Defenses	antibodies

Proteins are flexible

- conformational changes can be **small**
  (molecular vibrations, small movements of amino acids);
  "breathing"
- or relatively **large**
  structural domains moving several nm

"Induced fit": the complementarity-enhancing structural adaptation that occurs between protein and ligand

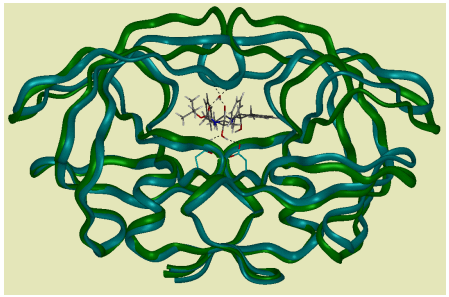


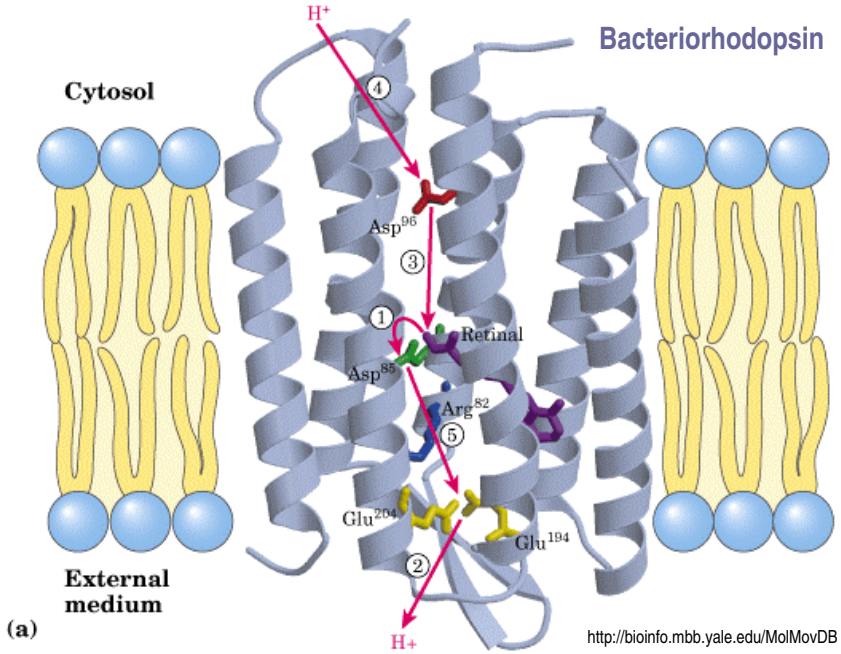
Conformational coupling: Ligand binding orients PBP receptor-binding face for signaling complex formation

I. Motions of Fragments Smaller than Domains

A. Motion is predominantly shear - Proteins for which two or more conformations are known: dihydrofolate reductase, insulin, thymidylate synthase, bacteriorhodopsin…

B. Motion is predominantly hinge - Proteins for which two or more conformations are known: annexin V (Trp motion), cystatin, enolase, HIV-1 protease, HhaI methyltransferase, immunoglobulin (CDR motion), isocitrate dehydrogenase, lactate dehydrogenase, lipase, malate dehydrogenase, seryl-tRNA synthetase, triglyceride lipase, triose phosphate isomerase, *Yersinia* protein tyrosine phosphatase, ras protein, recvinm ...

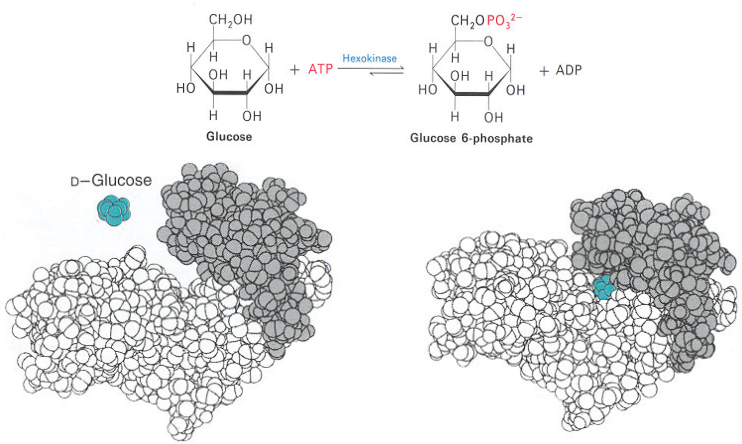




http://bioinfo.mbb.yale.edu/MolMovDB

II. Domain Motions

A. Motion is predominantly shear - Proteins for which two or more conformations are known: alcohol dehydrogenase, aspartate amino transferase, citrate synthase, endothiapepsin, glyceraldehyde-3-phosphate dehydrogenase, glycerol kinase, hexokinase, human interleukin 5, phosphofructokinase (not allosteric transition), Trp repressor…



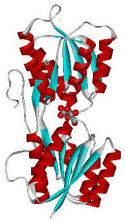
II. Domain Motions

B. Motion is predominantly hinge - Proteins for which two or more conformations are known: Acetylcholinesterase, adenylate kinase, annexin V (breathing motion), calbindin, calmodulin, canine lymphoma immunoglobulin (Fc-Fab hinge), catabolite gene activator protein (CAP), cell adhesion molecule CD2, DNA polymerase beta, diphtheria toxin, *E. coli.* periplasmic dipeptide binding protein, family-5 endoglucanase CelC, formate dehydrogenase, glutamate dehydrogenase, glutamine binding protein, GroEL domain, heat shock transcription factor, interferon-gamma, iron sulfur protein (bc1 complex), lactoferrin, Lysine/Arginine/Ornithine (LAO) binding protein, maltodextrin binding protein, phosphoglycerate kinase, recoverin, T4 lysozyme mutants (Ile3->Pro & Met6->Ile), TBSV coat protein, troponin-C, tryptophan synthase, c-Src tyrosine kinase, cAMP-dependent protein kinase (catalytic domain)…

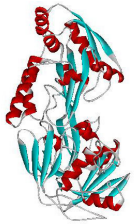
C. Motion involves partial refolding of tertiary structure - Proteins for which two or more conformations are known: Gα, HIV-1 reverse transcriptase, haemagglutinin, serpins…

Periplasmic Binding Proteins

a structurally conserved family of bilobate, soluble receptor proteins

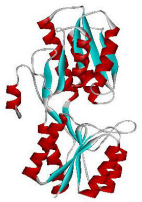


Glucose/Galactose Binding Protein

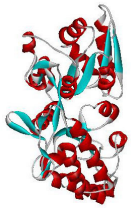


Dipeptide Binding Protein

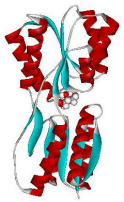
Leu, Ile, Val Binding Protein



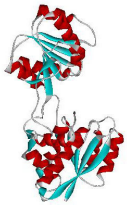
Arabinose Binding Protein



Maltose Binding Protein



Ribose Binding Protein

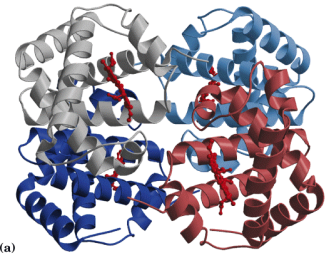


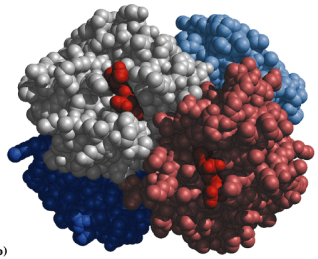
Leucine Binding Protein

D-Allose Binding Protein

III. Larger Movements than Domain Movements involving the Motion of Subunits

A. Motion involves an allosteric transition - Proteins for which two or more conformations are known: aspartate transcarbamoylase, fructose-1,6-biphosphatase, glycogen phosphorylase, hemoglobin, Lac repressor core (allosteric motion), Lac repressor upon binding DNA (subunit motion via tetramerization domain), phosphofructokinase…





B. Motion does not involve an allosteric transition - Proteins for which two or more conformations are known: aspartate receptor, Bam HI endonuclease, immunoglobulin (VL-VH movement), *S. cerevisiae* PPR1 Zn-finger DNA recognition protein, erythopoietin receptor, F1-ATPase, polymerase processivity factor PCNA…

Dynamics and Relaxation

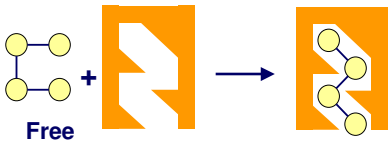
- **Time scales and molecular motions**

Atomic fluctuations, vibrations	10^{-15} to 10^{-12} s	< 1Å
Group motions (covalently linked units)	10^{-12} – 10^{-3} s	< 1 Å – 50 Å
Molecular rotation, reorientation	10^{-12} – 10^{-9} s	
Molecular translation, diffusion		
Rotation of methyl groups	10^{-12} – 10^{-9} s	
Flips of aromatic rings	10^{-9} – 10^{-6} s	
Domain motions	10^{-8} – 10^{-3} s	
Proline isomerization	> 10^{-3} s	

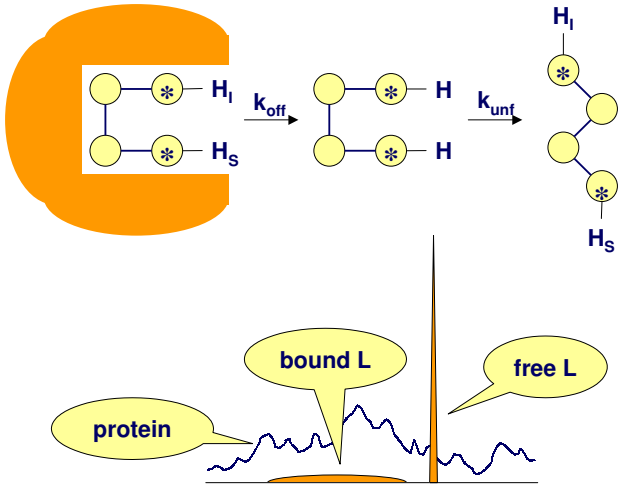
Chemical exchange (*e.g.* two protein conformations)
Amide exchange
Ligand binding

- **Time scales and molecular motions**

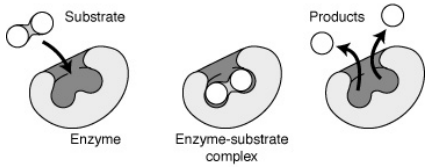
Atomic fluctuations, vibrations	Influences bond length measurements
Group motions (covalently linked units)	
Molecular rotation, reorientation	Relaxation, linewidths, correlation times
Molecular translation, diffusion	DOSY NMR
Rotation of methyl groups	^{2}H NMR
Flips of aromatic rings	^{2}H NMR
Domain motions	^{2}H NMR
Chemical exchange, Pro isomerization	Chemical shifts
Amide exchange	^{15}N-^{1}H HSQC
Ligand binding	Transferred NOE measurements



Transferred NOEs



Enzymes: A special case of protein function

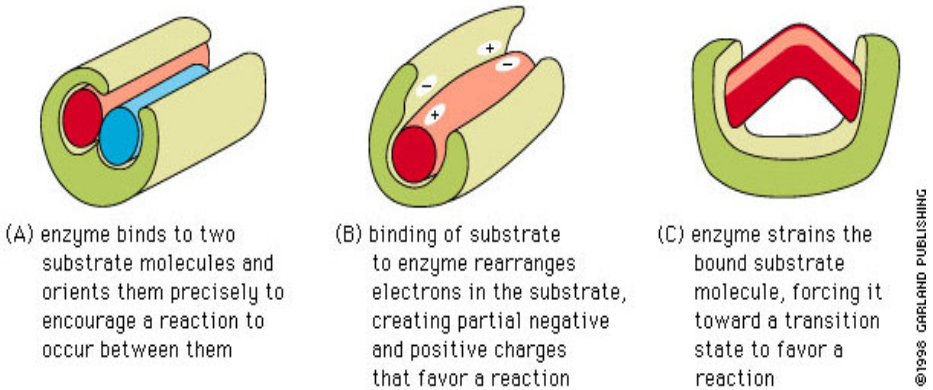


Enzymes bind and assist in the chemical transformation of other molecules

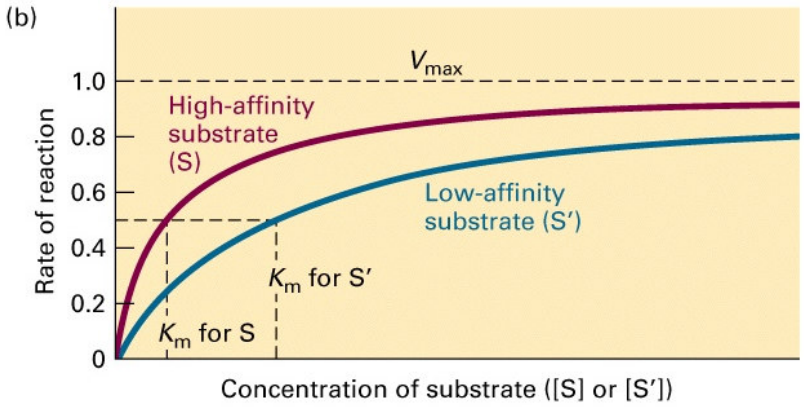
Substrate: molecule acted upon by an enzyme (analogous to ligand)

Catalytic site: substrate-binding site (analogous to ligand-binding site)

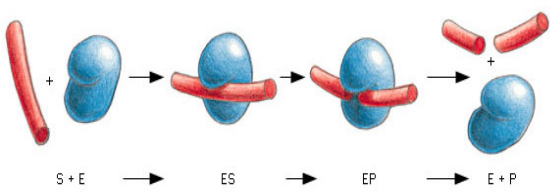
How do enzymes catalyze reactions?



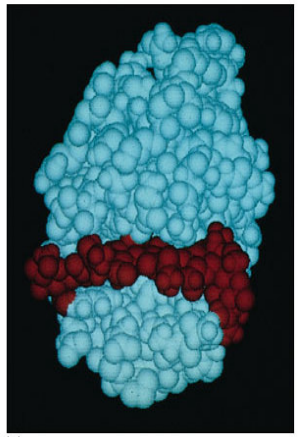
Kinetics of an enzymatic reaction are described by V_{max} and K_m



Lysozyme catalyzes the cutting of a polysaccharide chain

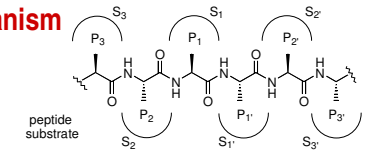


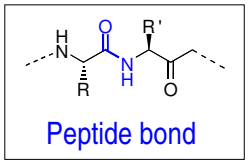
(A)



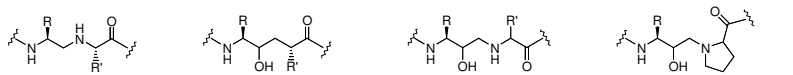
(B)

Hydrolytic mechanism in HIV-1 protease





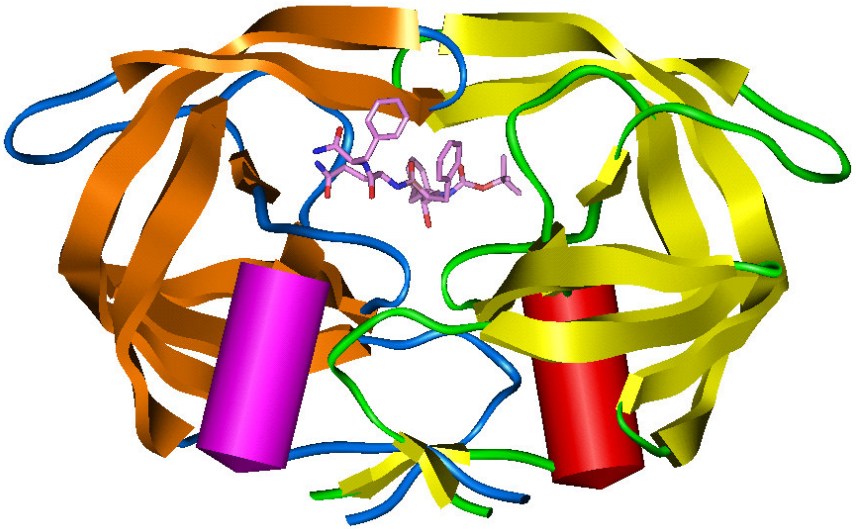
Examples of non-hydrolyzable isosteres of the peptide bond cleaved by HIV-1 protease



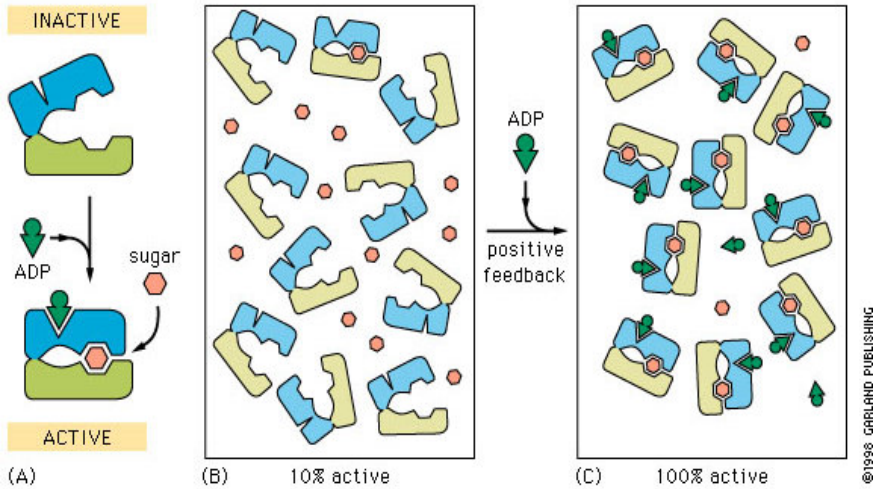
Reduced amide | Hydroxyethylene | Hydroxyethylamine (acyclic R') | Hydroxyethylamine (cyclic R')

Norstatine | Mono-ol | Diol | Azapeptide

HIV-1 protease in complex with inhibitor QF-34

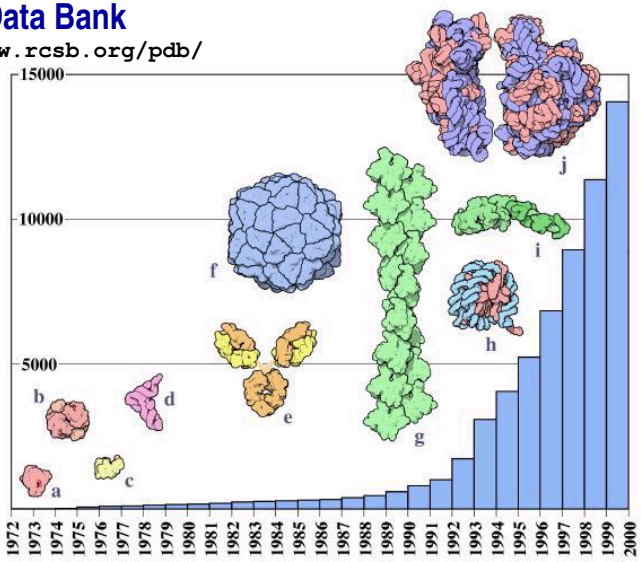


Enzyme activation caused by an allosteric change



Protein Data Bank

http://www.rcsb.org/pdb/



(a) myoglobin (b) hemoglobin (c) lysozyme (d) transfer RNA
(e) antibodies (f) viruses (g) actin (h) the nucleosome
(i) myosin (j) the ribosome

Courtesy of David Goodsell, TSRI

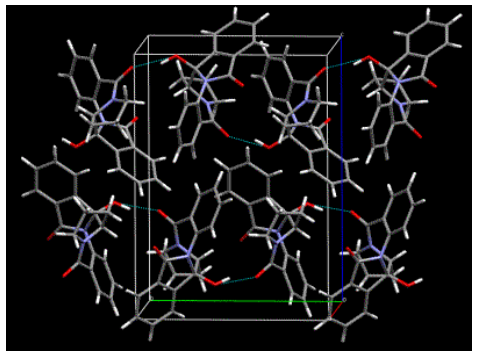
Cambridge Structural Database

The Cambridge Crystallographic Data Centre (CCDC) builds, maintains and distributes the Cambridge Structural Database (CSD), a searchable database of organic and metallo-organic crystal structures.

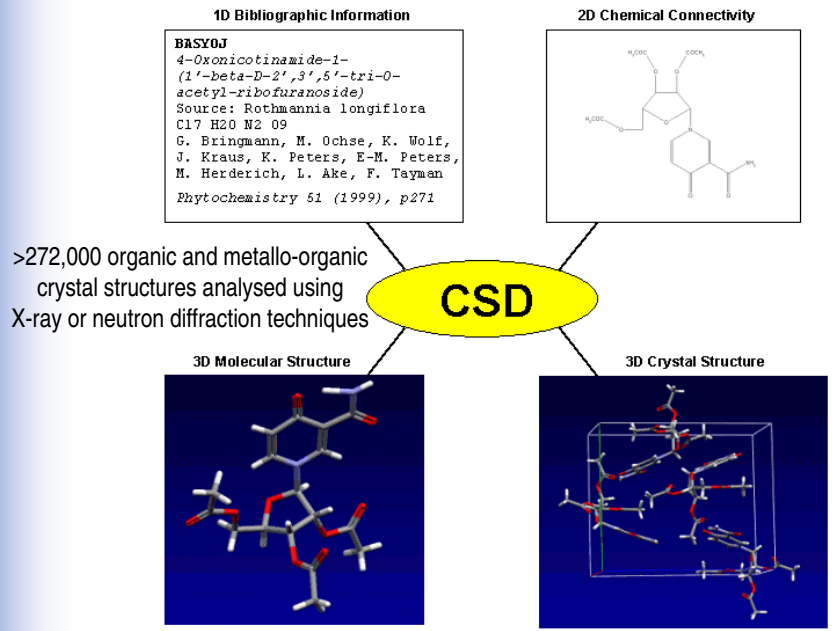
The CCDC also produce and distribute software products which make use of the data contained in the CSD.

http://www.ccdc.cam.ac.uk/

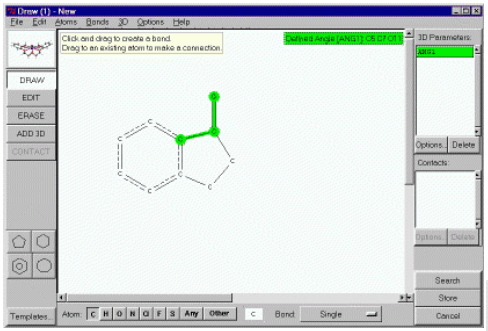
Increasing the Value of Crystallographic Databases



- Derived knowledge bases
- Knowledge-based applications programs
- Data mining tools for protein -ligand complexes

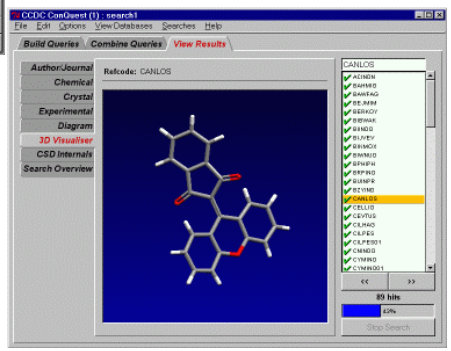


ConQuest



ConQuest provides a full range of text/numeric database search options, in addition to more complex search functionality, including:

- **Chemical substructure searching**
- **Geometrical searching**
- **Intermolecular non-bonded contact searching**



Cambridge Crystallographic Data Centre

http://www.ccdc.cam.ac.uk/

```
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137C                                                                          9220
R=0.                                                                          5620
211                                                                           3700
C  6                                                                          1260
I1                                                                            4940
C2                                                                            4730
C5                                                                            3960
C8                                                                            7280
C10                                                                           2420
H3
H6
H9
H12
H15
 0 3
HEADER    CSD ENTRY DOXSIS
COMPND    NICOTINE MONOHYDROGEN IODIDE
CRYST    13.705    9.974    8.436  90.00  90.00  90.00 P212121
ATOM      1  I1  NICO    1        1.583   1.561   0.355  1.00  0.00
ATOM      2  N1  NICO    1        5.355  -5.377  10.252  1.00  0.00
ATOM      3  C1  NICO    1        5.744  -4.111  10.057  1.00  0.00
ATOM      4  C2  NICO    1        5.375  -3.343   8.953  1.00  0.00
ATOM      5  C3  NICO    1        4.573  -3.927   7.982  1.00  0.00
ATOM      6  C4  NICO    1        4.180  -5.249   8.151  1.00  0.00
ATOM      7  C5  NICO    1        4.584  -5.922   9.302  1.00  0.00
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ATOM      9  C7  NICO    1        4.752  -0.841   8.748  1.00  0.00
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ATOM     11  C9  NICO    1        6.826  -0.125   7.655  1.00  0.00
ATOM     12  N2  NICO    1        6.722  -1.627   7.699  1.00  0.00
....
CONECT    1    0
CONECT    2    3    7
CONECT    3    2    4   14
....
MASTER        0    0    0    0    0    0    0    0   28    0   28    0
END
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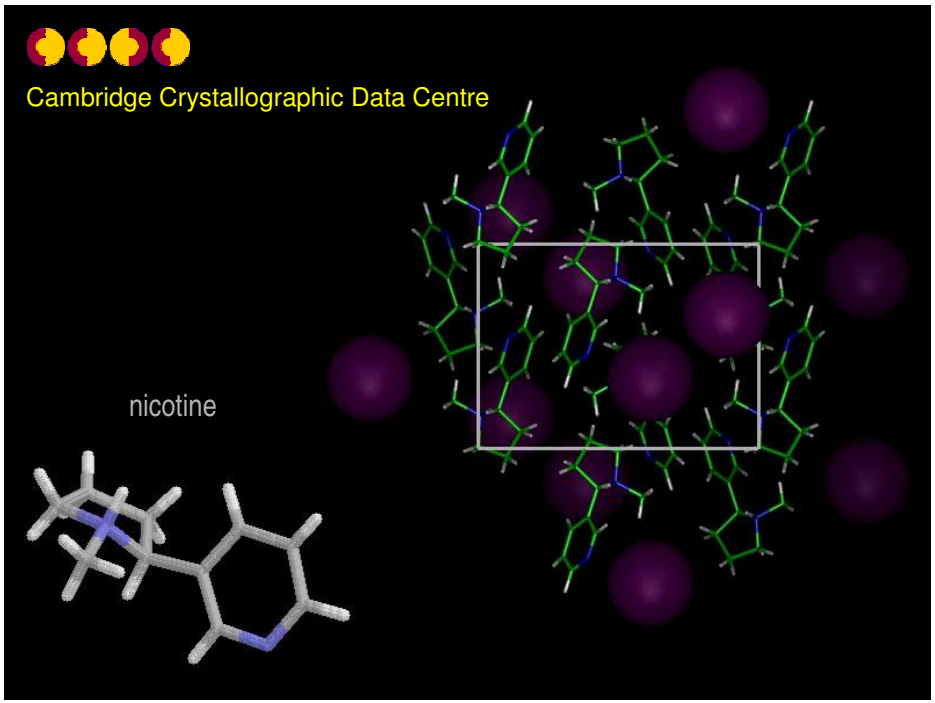
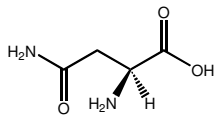
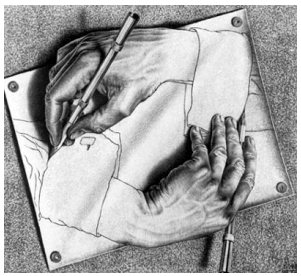


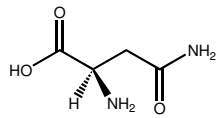
The Importance of Chirality



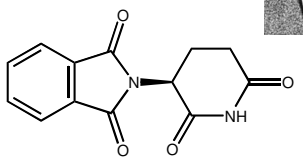
Bitter

Asparagine



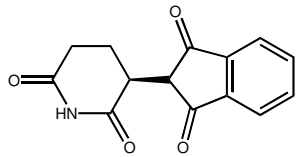


Sweet



Extreme teratogen

Thalidomide



Anti-morning sickness

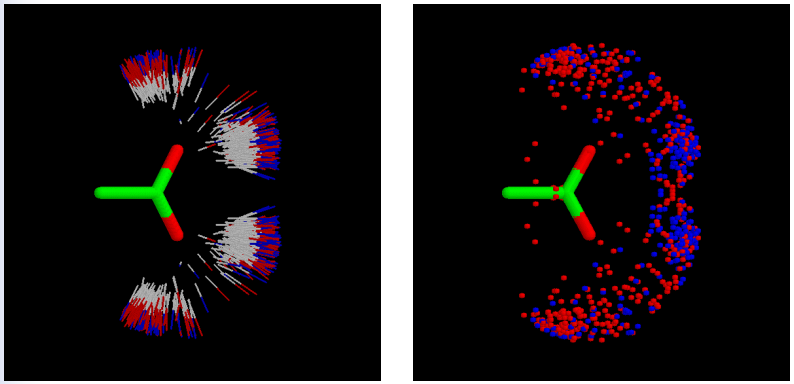
IsoStar and SUPERSTAR

IsoStar - knowledge base of information about intermolecular interactions

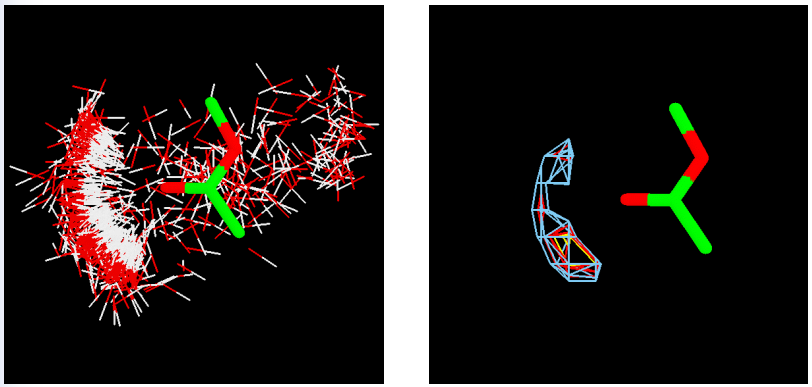
SuperStar - program for predicting binding points in an enzyme active site

SuperStar predictions based solely on **IsoStar** data

IsoStar Scatterplots



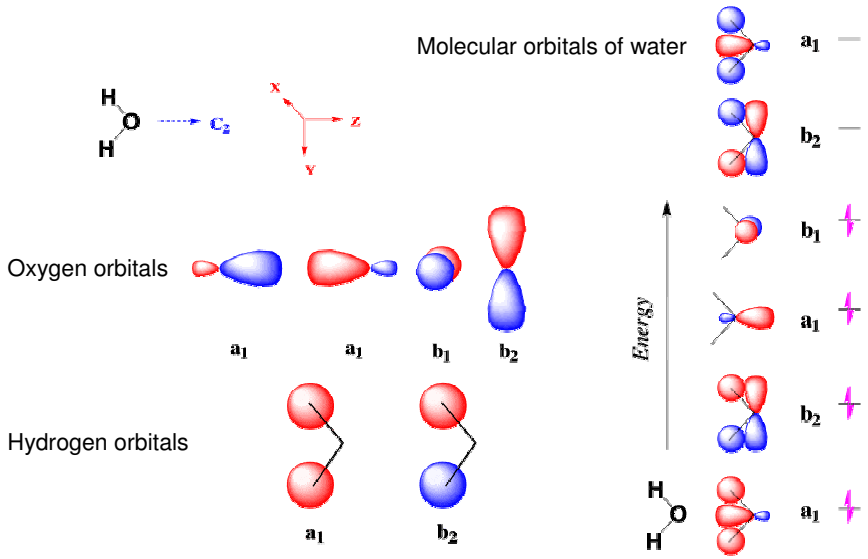
IsoStar Density Surfaces



A probability surface derived from the observed positions of hydrogen-bonding hydrogen atoms around aliphatic esters.

Quantum Chemistry

Atomic orbitals can be combined to give molecular orbitals



Ab initio METHODS

* Hartree-Fock method

* Electron correlation methods

❧ variational methods

Configuration Interaction with double excitations (CID)

Configuration Interaction with single and double excitations (CISD)

❧ perturbation methods

Møller and Plesset (MP2, MP3, MP4)

Quadratic Convergence CI method (QCISD)

❧ density functional methods (DFT)

BP86 - developed by Becke and Perdew in 1986

BLYP - developed by Becke, Lee, Yang and Parr

B3LYP - a modification of BLYP in which a 3-parameter functional developed by Axel Becke is used.

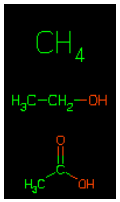
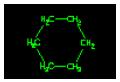
SMILES

Simplified Molecular Input Line Entry Specification

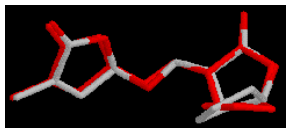
Rules

1. Atoms are represented by atomic symbols: B, C, N, O, F, P, S, Cl, Br, and I.
2. Double bonds are `=' , triple bonds are `#' .
3. Branching is indicated by parentheses.
4. Ring closures are indicated by pairs of matching digits.

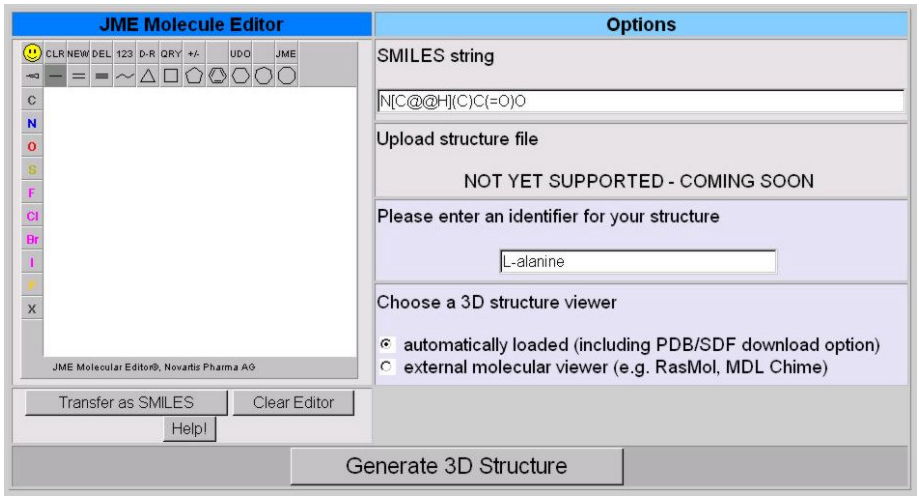
Examples

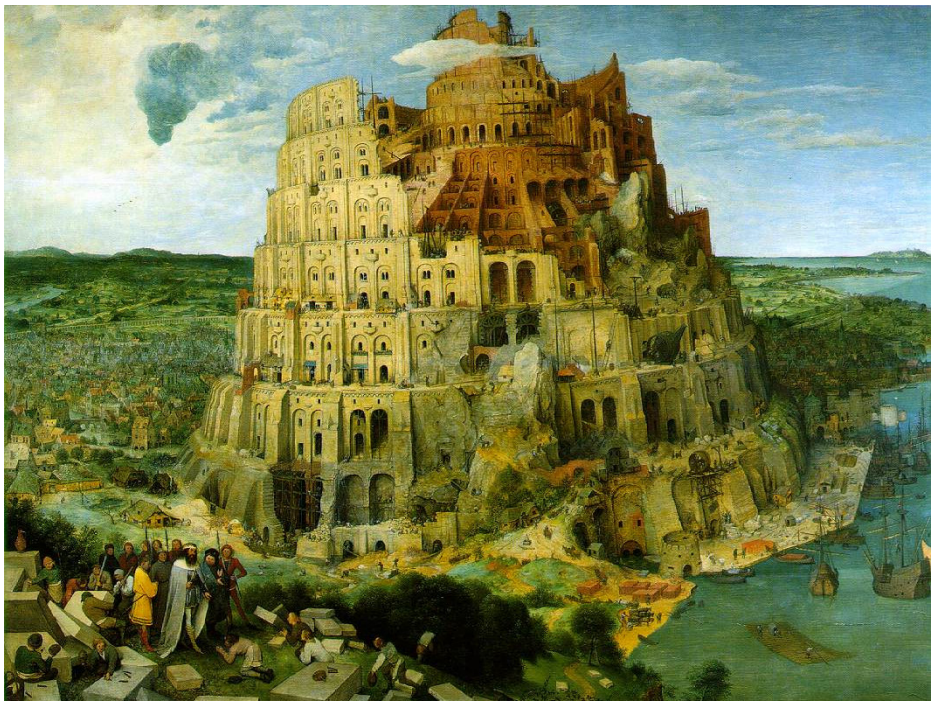
Depiction	SSMILES	Name	Remark
	C	methane	hydrogens fill normal valence
	CCO	ethanol	a single bond is assumed to join adjacent atoms
	CC(=O)O	acetic acid	parentheses are used to indicate branching
	C1CCCCC1	cyclohexane	bonds can also be represented by pairs of matching digits

Automatic generation of three-dimensional atomic COoRdINAtes



http://www2.chemie.uni-erlangen.de/software/corina/free_struct.html





BABEL A program designed to interconvert a number of file formats currently used in molecular modelling

Input type codes:

```
alc -- Alchemy file
prep -- AMBER PREP file
bs -- Ball and Stick file
bgf -- MSI BGF file
car -- Biosym .CAR file
boog -- Boogie file
caccrt -- Cacao Cartesian file
cadpac -- Cambridge CADPAC file
charmm -- CHARMm file
c3d1 -- Chem3D Cartesian 1 file
c3d2 -- Chem3D Cartesian 2 file
cssr -- CSD CSSR file
fdat -- CSD FDAT file
gstat -- CSD GSTAT file
dock -- Dock Database file
dpdb -- Dock PDB file
feat -- Feature file
fract -- Free Form Fractional file
gamout -- GAMESS Output file
gzmat -- Gaussian Z-Matrix file
gauout -- Gaussian 92 Output file
g94 -- Gaussian 94 Output file
gr96A -- GROMOS96 (A) file
gr96N -- GROMOS96 (nm) file
hin -- Hyperchem HIN file
sdf -- MDL Isis SDF file
m3d -- M3D file
macmol -- Mac Molecule file
macmod -- Macromodel file
micro -- Micro World file
mm2in -- MM2 Input file
mm2out -- MM2 Output file
mm3 -- MM3 file
mmads -- MMADS file
mdl -- MDL MOLfile file
molen -- MOLIN file
mopcrt -- Mopac Cartesian file
mopint -- Mopac Internal file
mopout -- Mopac Output file
pcmod -- PC Model file
pdb -- PDB file
psin -- PS-GVB Input file
psout -- PS-GVB Output file
msf -- Quanta MSF file
schakal -- Schakal file
shelx -- ShelX file
smiles -- SMILES file
spar -- Spartan file
semi -- Spartan Semi-Empirical file
spmm -- Spartan Mol. Mechanics file
mol -- Sybyl Mol file
mol2 -- Sybyl Mol2 file
wiz -- Conjure file
unixyz -- UniChem XYZ file
xyz -- XYZ file
xed -- XED file
```

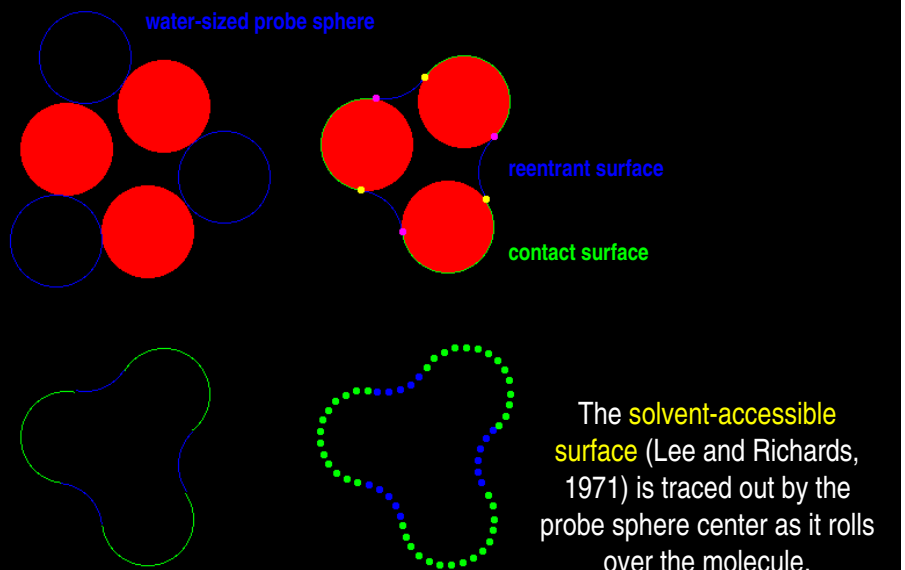
BABEL A program designed to interconvert a number of file formats currently used in molecular modelling

Output type codes:

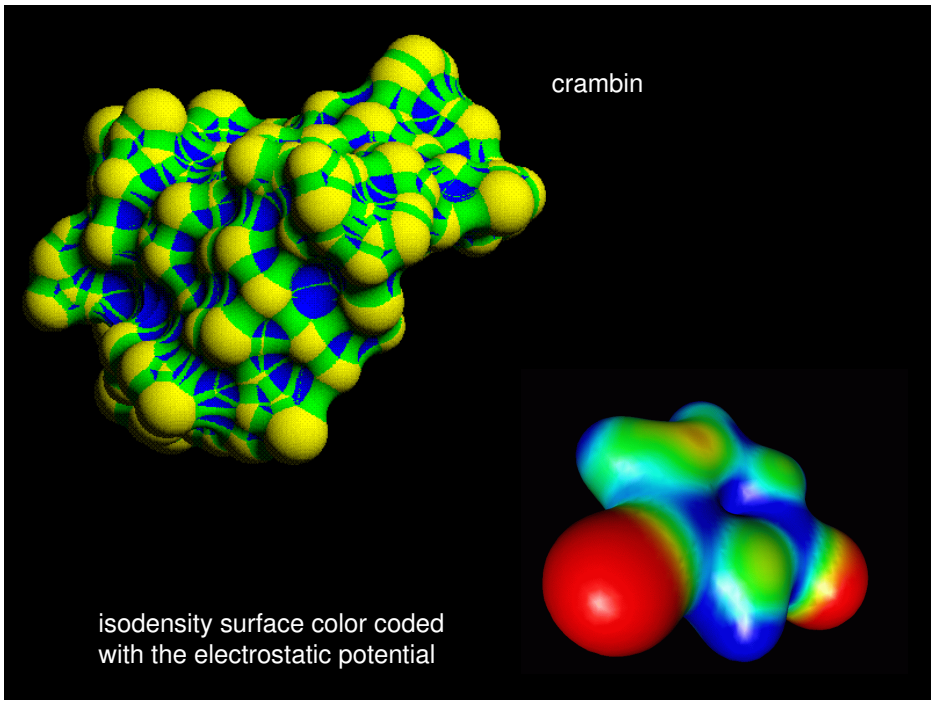
```
diag -- DIAGNOTICS file
t -- Alchemy file
bs -- Ball and Stick file
bmin -- Batchmin Command file
caccrt -- Cacao Cartesian file
cacint -- Cacao Internal file
cache -- CAche MolStruct file
c3d1 -- Chem3D Cartesian 1 file
c3d2 -- Chem3D Cartesian 2 file
d -- ChemDraw Conn. Table file
con -- Conjure file
contmp -- Conjure Template file
cssr -- CSD CSSR file
feat -- Feature file
fhz -- Fenske-Hall ZMatrix file
gamin -- Gamess Input file
gcart -- Gaussian Cartesian file
g -- Gaussian Z-matrix file
gotmp -- Gaussian Z-matrix tmplt file
hin -- Hyperchem HIN file
icon -- Icon 8 file
i -- IDATM file
macmol -- Mac Molecule file
k -- Macromodel file
micro -- Micro World file
mi -- MM2 Input file
mo -- MM2 Ouput file
mm3 -- MM3 file
mmads -- MMADS file
mdl -- MDL Molfile file
ac -- Mopac Cartesian file
ai -- Mopac Internal file
pc -- PC Model file
p -- PDB file
report -- Report file
spar -- Spartan file
mol -- Sybyl Mol file
mol2 -- Sybyl Mol2 file
maccs -- MDL Maccs file file
xed -- XED file
unixyz -- UniChem XYZ file
x -- XYZ file
```

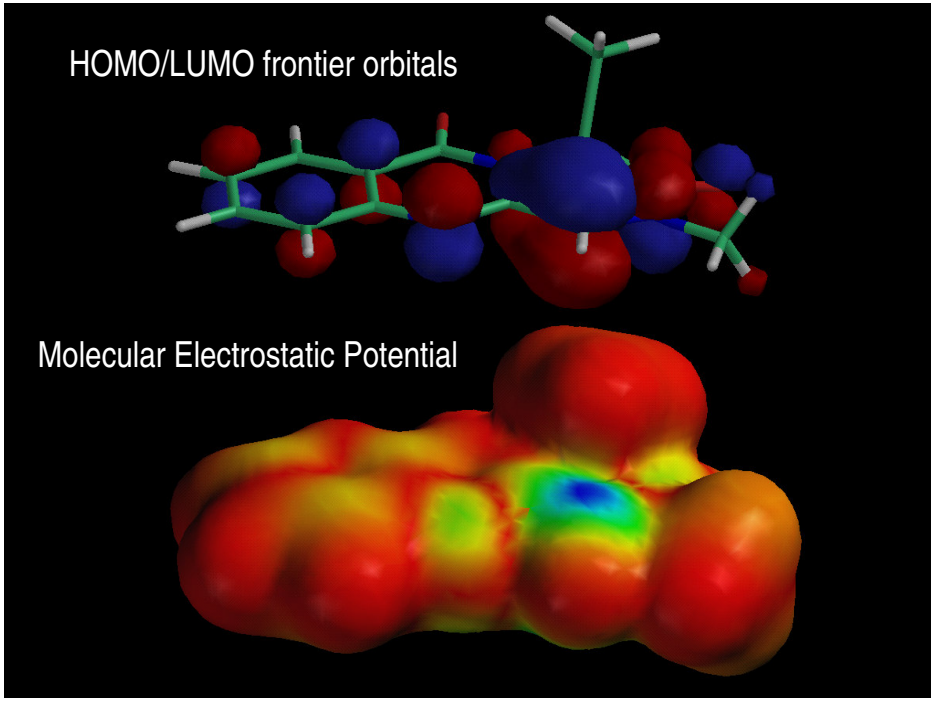
ftp://ccl.osc.edu/pub/chemistry/software/UNIX/babel/

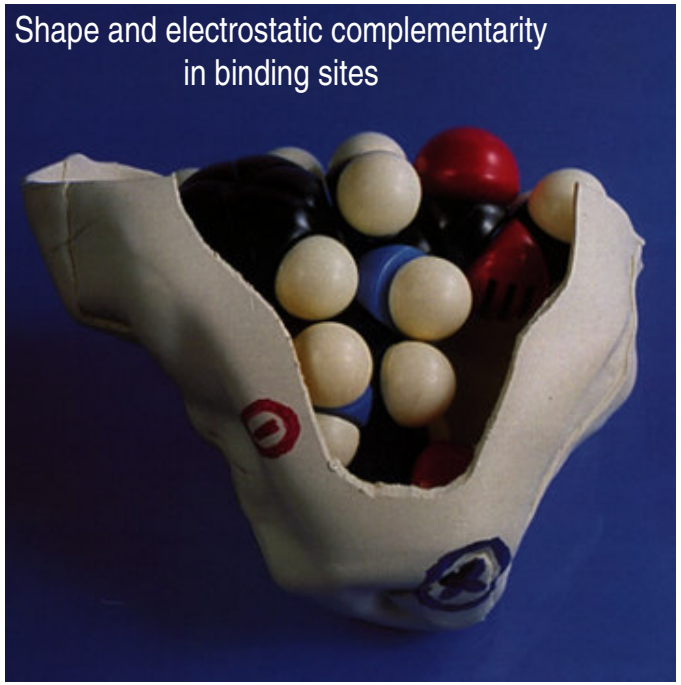
Molecular Surfaces

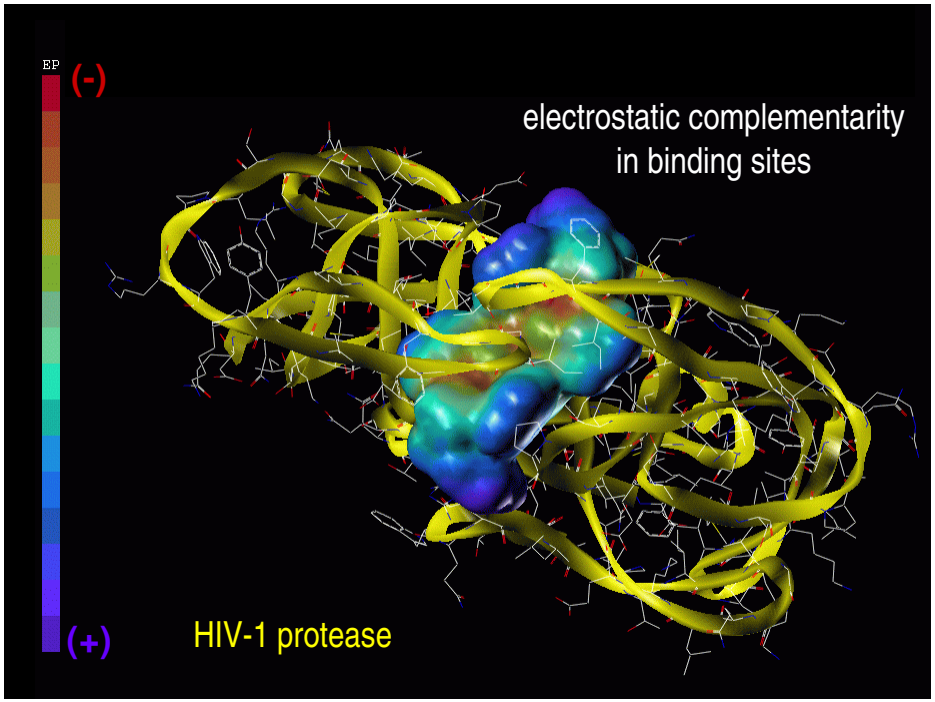


The solvent-accessible surface (Lee and Richards, 1971) is traced out by the probe sphere center as it rolls over the molecule.









MOLECULAR MECHANICS (MM)

➳ A computational technique used to model the conformational behaviour and energetic properties of molecules.

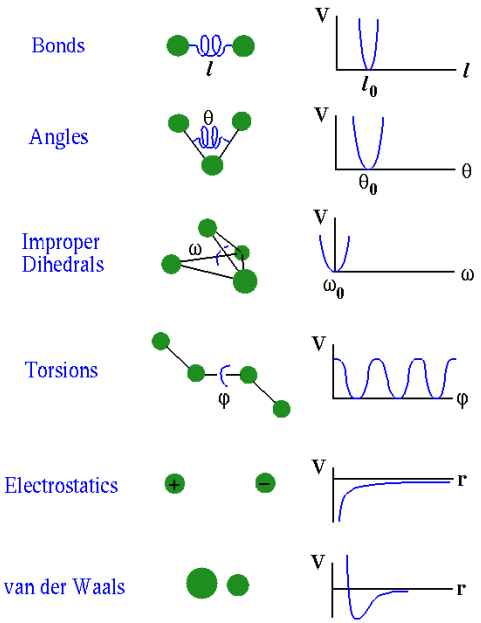
➳ The molecule is treated at the atomic level, i.e. the electrons are not treated explicitly.

➳ MM uses an Energy Function, defined so that given a particular conformation, (i.e. given a set of spatial coordinates for all the atoms) the energy of the molecule can be calculated.

➳ The energy function is empirical, i.e. it is not entirely derived from rigorous theories.

➳ The energy function makes a distinction between 'bonded' and 'non-bonded' interactions.

Empirical Potential Energy Function



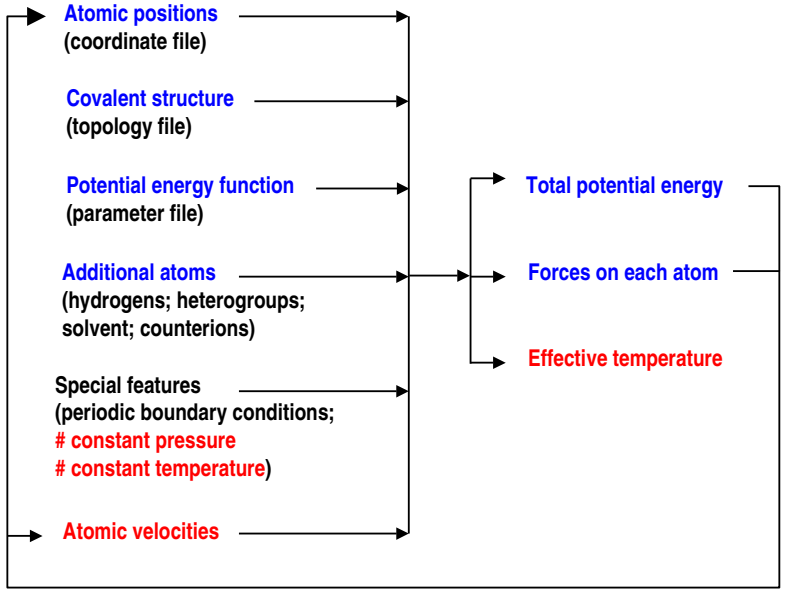
Summary of interactions included in a representative molecular mechanics **force field**

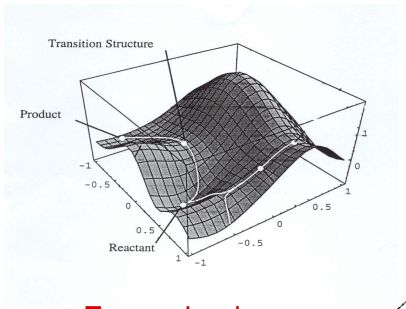
$$E_{total} = \sum_{bonds} K_r(r - r_{eq})^2 + \sum_{angles} K_\theta(\theta - \theta_{eq})^2 + \sum_{dihedrals} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)] + \sum_{i<j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\varepsilon R_{ij}}\right] + \sum_{H-bonds} \left[\frac{C_{ij}}{R_{ij}^{12}} - \frac{D_{ij}}{R_{ij}^{10}}\right]$$

➳ The empirical potential energy function is differentiable with respect to the atomic coordinates.

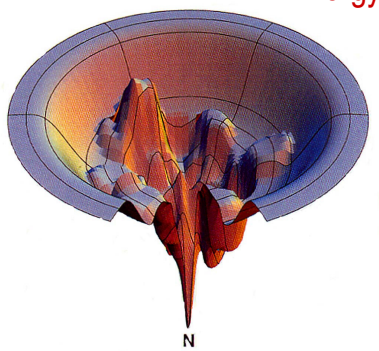
➳ This gives the value and the direction of the force acting on each atom and can thus be used in a molecular dynamics simulation.

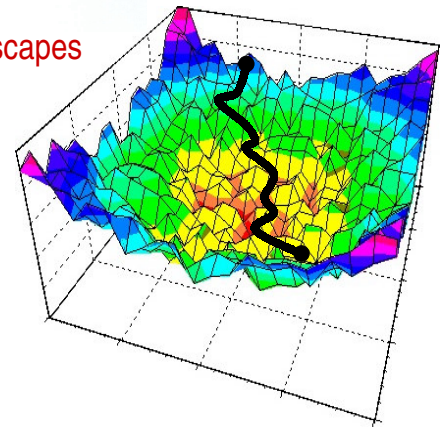
ALGORITHMS FOR ENERGY MINIMIZATION AND MOLECULAR DYNAMICS

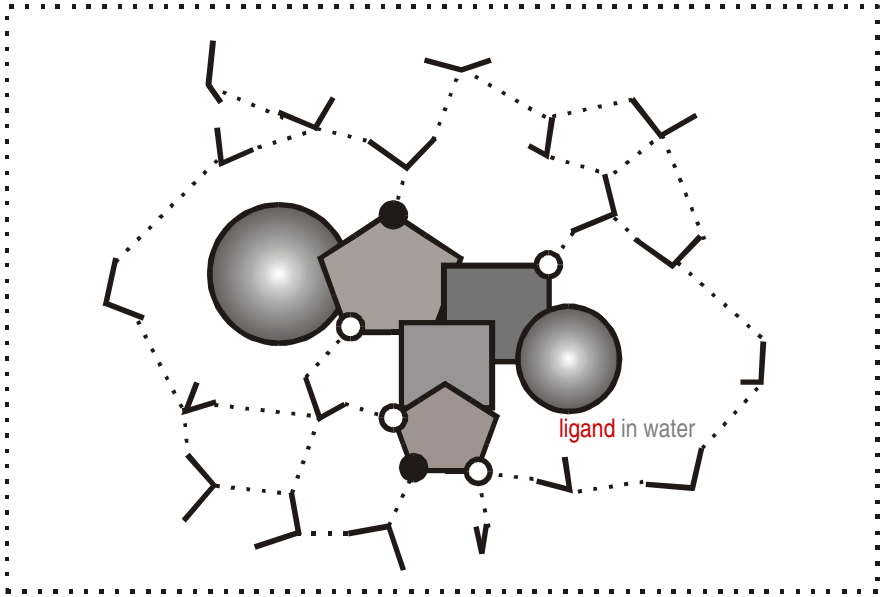


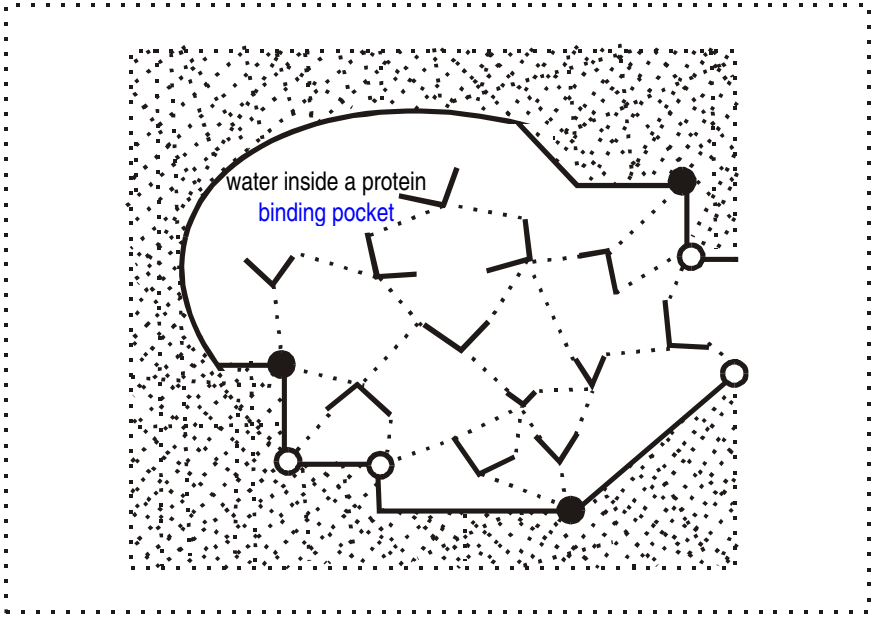


Energy landscapes

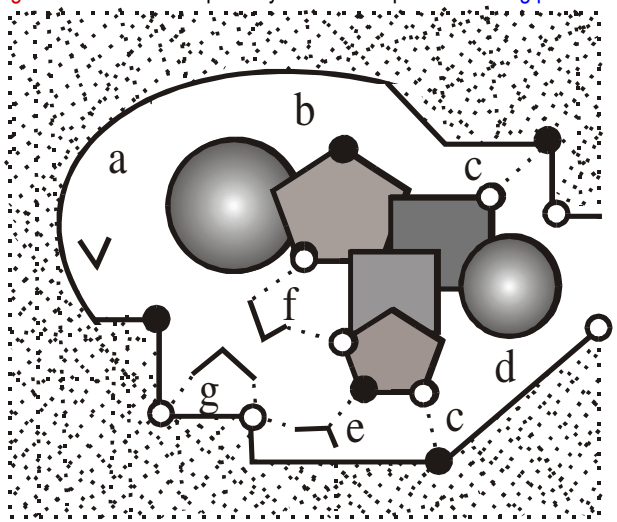




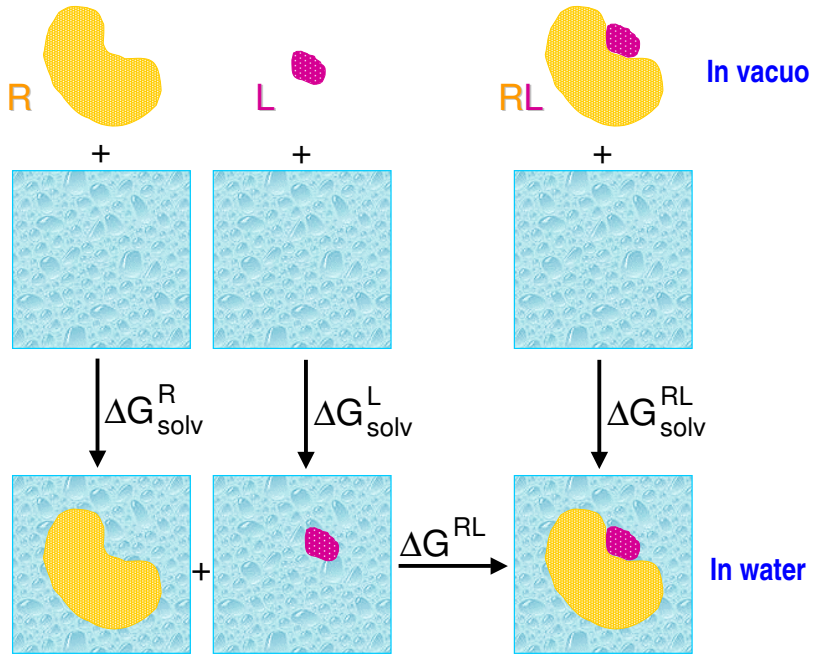




ligand buried inside a partially desolvated protein binding pocket



Conclusion: Any comprehensive method that attempts to model ligand binding must also consider the energy of solvation and entropic contributions to the binding process.



"DelPhi - A Macromolecular Electrostatics Modelling Package":

Kim A. Sharp, Anthony Nicholls & Barry Honig
Department of Biochemistry and Molecular Biophysics, Columbia University, New York

- Klapper, I.; Hagstrom, R.; Fine, R.; Sharp, K.; Honig, B. "Focusing of Electric Fields in the Active Site of Cu-Zn Superoxide Dismutase: Effects of Ionic Strength and Amino-acid Modification." *Proteins (1986) 1, 47-59.*

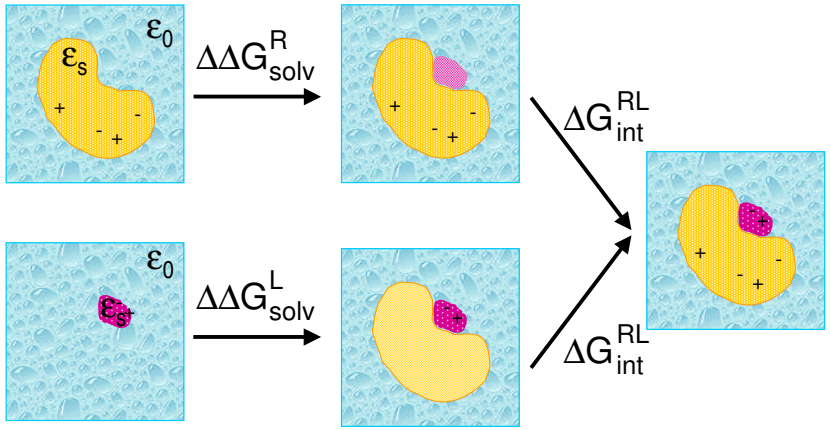
- Gilson, M. K.; Sharp, K. A.; Honig, B. H. "Calculating the Electrostatic Potential of Molecules in Solution: Method and Error Assessment" *J. Comput. Chem. (1987) 9, 327-335.*

- Gilson, M. K.; Honig, B. "Calculation of the Total Electrostatic Energy of a Macromolecular System: Solvation Energies, Binding Energies, and Conformational Analysis." *Proteins (1988) 4, 7-18.*

- K. Sharp, K.; Honig, B. "Electrostatic Interactions in Macromolecules: Theory and Applications." *Ann. Rev. Biophys. Biopys. Chem. (1990) 19, 301-332.*

- Nicholls, A.; Honig, B. "A Rapid Finite Difference Algorithm, Utilizing Successive Over-Relaxation to Solve the Poisson-Boltzmann Equation." *J. Comput. Chem. (1991) 12, 435-445.*

The original reference to the use of the finite difference method for macromolecular electrostatics is: J. Warwicker and H. C. Watson, *J. Mol. Biol. (1982) 157, 671.*



Affinity *vs.* Specificity

$$\text{Ligand} + \text{Receptor} \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} \text{Ligand-Receptor}$$

$$K_d = \frac{k_{off}}{k_{on}} = \frac{[\text{Ligand}]\,[\text{Receptor}]}{[\text{Ligand-Receptor}]}$$

$$\Delta G = \Delta H - T\Delta S$$

Binding constant ΔK_d	Binding energy ΔG (kcal/mol)
2x	0.5
5x	1.0
13x	1.5
29x	2.0
68x	2.5
158x	3.0

$$\Delta G = 2.303\ RT \log K_d$$

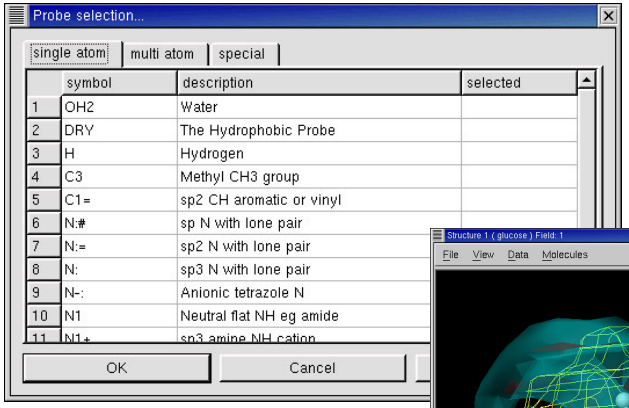
"GRID: A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules"

Peter Goodford, Oxford University

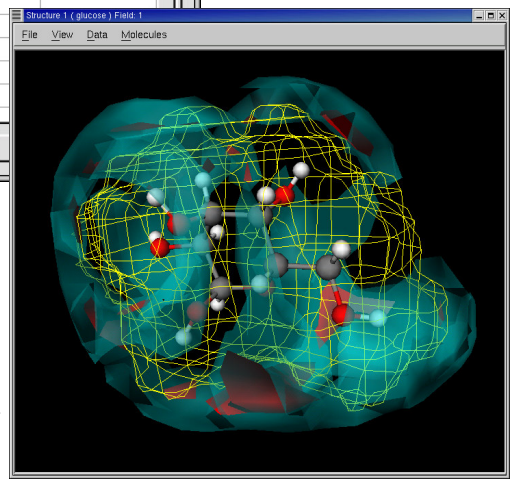
J. Med. Chem. 28, 849-857 (1985)
ibid. 32, 1083-1094 (1989); *36,* 140-147 (1993); *36,* 148-156 (1993)

Molecular Discovery

http://www.moldiscovery.com/



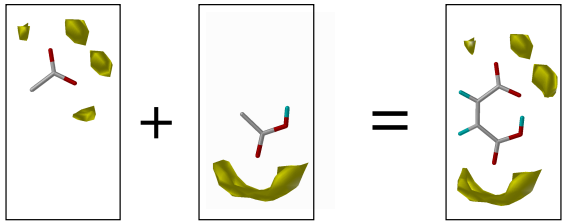
GRID v. 21



Molecular Discovery

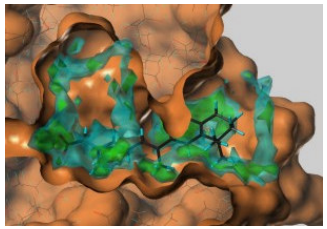
http://www.moldiscovery.com/

SuperStar



- Calculate binding positions for specific probe atoms in protein active sites
- Identify functional groups in binding-site
- Look up relevant IsoStar scatterplots and overlay on functional groups
- Contour - combining by taking products

SuperStar Features



map for aromatic CH carbon probe generated at the binding site of the protein-ligand complex 1CPS

- Cavity detection
- Surface or pharmacophore point display
- Metal coordination
- Hyperlinking to IsoStar scatterplots
- Choice of CSD- or PDB-based maps
- Gaussian fits

Relibase+

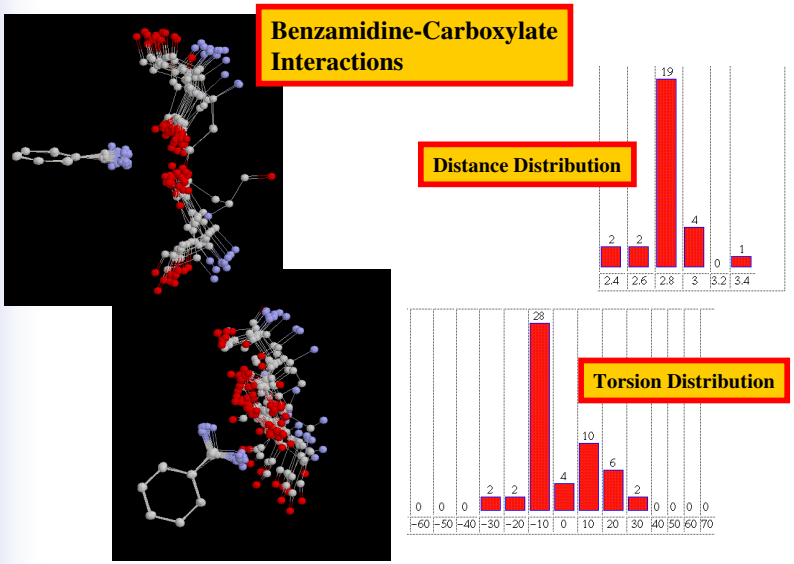
- **Protein-ligand database system**
- **Based on original software developed by Manfred Hendlich and colleagues at Merck and Marburg University**
- **Enables searching of PDB and of in-house proprietary databases**

Relibase: http://relibase.ccdc.cam.ac.uk/

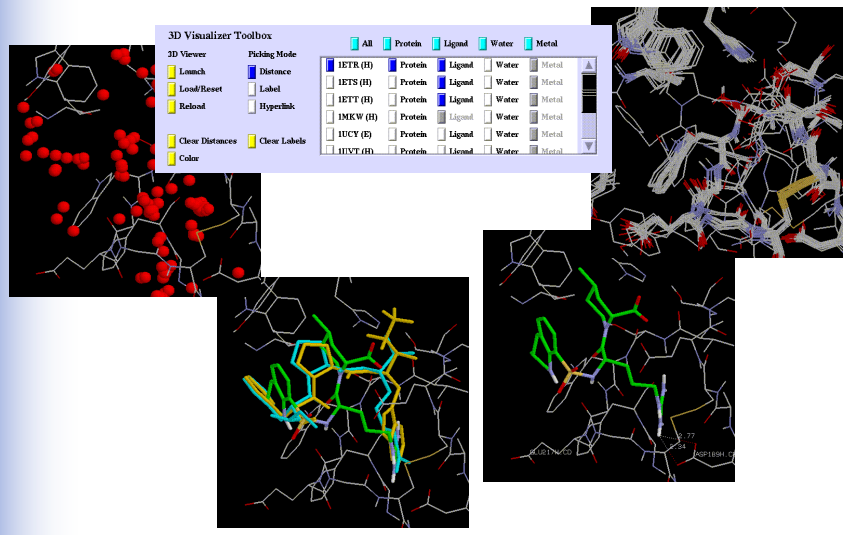
Some Relibase+ options

- Text searching
- Sequence searching
- 2D substructure and similarity searching
- 3D substructure searching
- Logical combination of hit lists
- Searching for intermolecular interactions
- Auto-superposition of similar binding sites
- Scripting facility based on Python

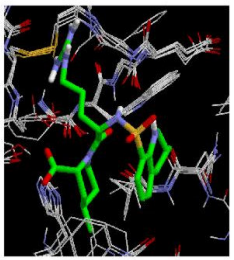
Analysis of 3D Queries



Binding Site Superposition



Relibase



Relibase: A program for searching protein-ligand databases.

Version 4.0, October 2000

Relibase is copyright Manfred Hendlich 1994-1999 and Cambridge Crystallographic Data Centre 1999, 2000.

Install 3D visualization software

Comments/bugs/queries to:

Cambridge Crystallographic Data Centre
12 Union Road
Cambridge CB2 1EZ
United Kingdom
tel: (44) (1223) 336022
e-mail: support@ccdc.cam.ac.uk

http://relibase.ccdc.cam.ac.uk/

http://relibase.ebi.ac.uk/

http://relibase.rutgers.edu/

LIGPLOT

http://www.biochem.ucl.ac.uk/bsm/ligplot/ligplot.html

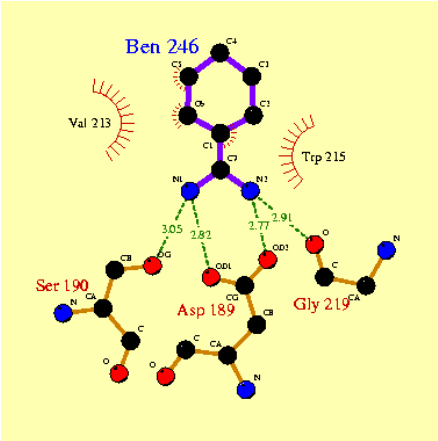
Program for automatically plotting protein-ligand interactions (by A. Wallace & R. Laskowski)

Automatically generates schematic diagrams of protein-ligand interactions for a given PDB file.

hydrogen bonds: dashed lines between the atoms involved.

hydrophobic contact: an arc with spokes radiating towards the ligand atoms they contact. The contacted atoms are shown with spokes radiating back.

Atom accessibilities can also be depicted; the ligand atoms can be colour-coded to indicate their accessibility to solvent.

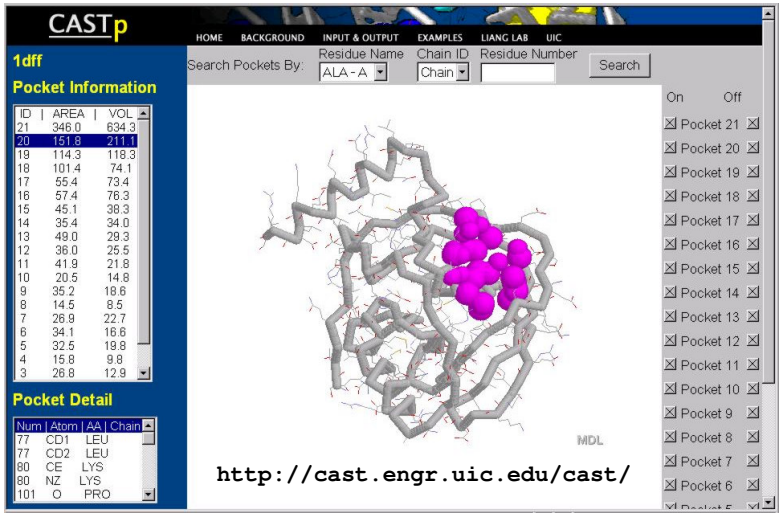


benzamidine (PDB code 2TBS)

CASTp

A Server for Identification of Protein Pockets & Cavities

- Identifies all pockets and cavities.
- Measures the volume and area analytically.



Ligand Protein Database

http://lpdb.scripps.edu

variables		VIP*
numberofhydrogenandionicbonds	1.50	
interactionsurfacearea(Å ²)	1.31	
calculatedmolecularrefractivity(ligand)	1.3	1
molecularweight(ligand)		1.29
numberofatoms(ligand)		1.28
numberofdonors(ligand)		1.20
numberofrotatablebonds(ligand)	1.1	6
numberofacceptors(ligand)		1.14
ClogP(ligand)		1.01

* variable influence on projection parameter

O. Roche, R. Kiyama & C. L. Brooks
J. Med. Chem. **44**, 3592-3598 (2001)

Break - Descanso

Top 10 ways to tell you drink too much coffee

10 Juan Valdéz names his donkey after you
9 You get a speeding ticket even when you' re parked
8 You grind your coffee beans in your mouth
7 You sleep with your eyes open
6 You watch videos in fast-forward
5 You lick your coffeepot clean
4 Your eyes stay open when you sneeze
3 The nurse needs a scientific calculator to take your pulse
2 You can type sixty words a minute with your feet
1 You can jump-start your car without jumper cables.