

Molecular Surface Representation

Applications to docking

Motivation

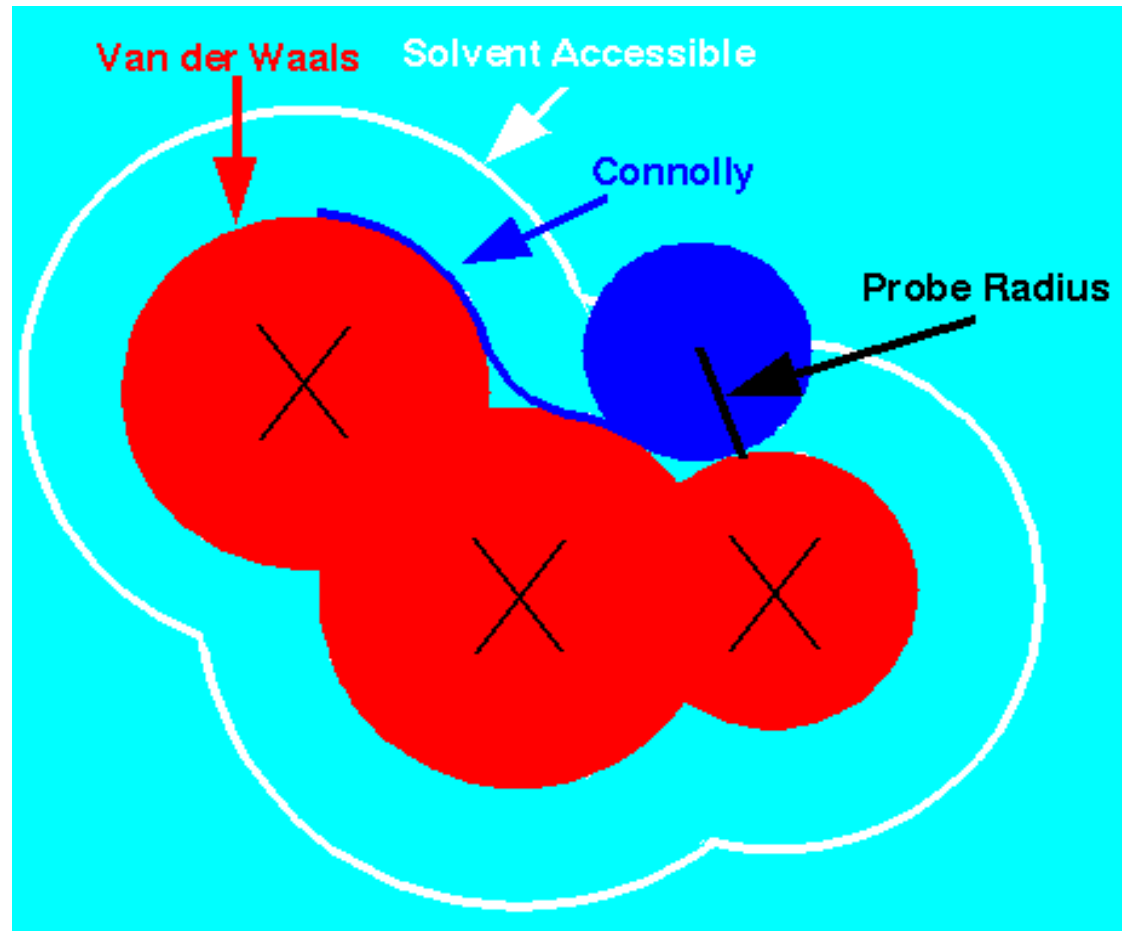
- **Studies of protein folding (Lee and Richards).**
- **Prediction of biomolecular recognition.**
- **Detection of drug binding ‘cavities’.**
- **Molecular Graphics.**

Comprehensive on-line Review

- **Michael L. Connolly**, *Molecular Surfaces: A Review* :

<http://www.netsci.org/Science/Compchem/feature14.html>

Solvent Accessible Surface - SAS



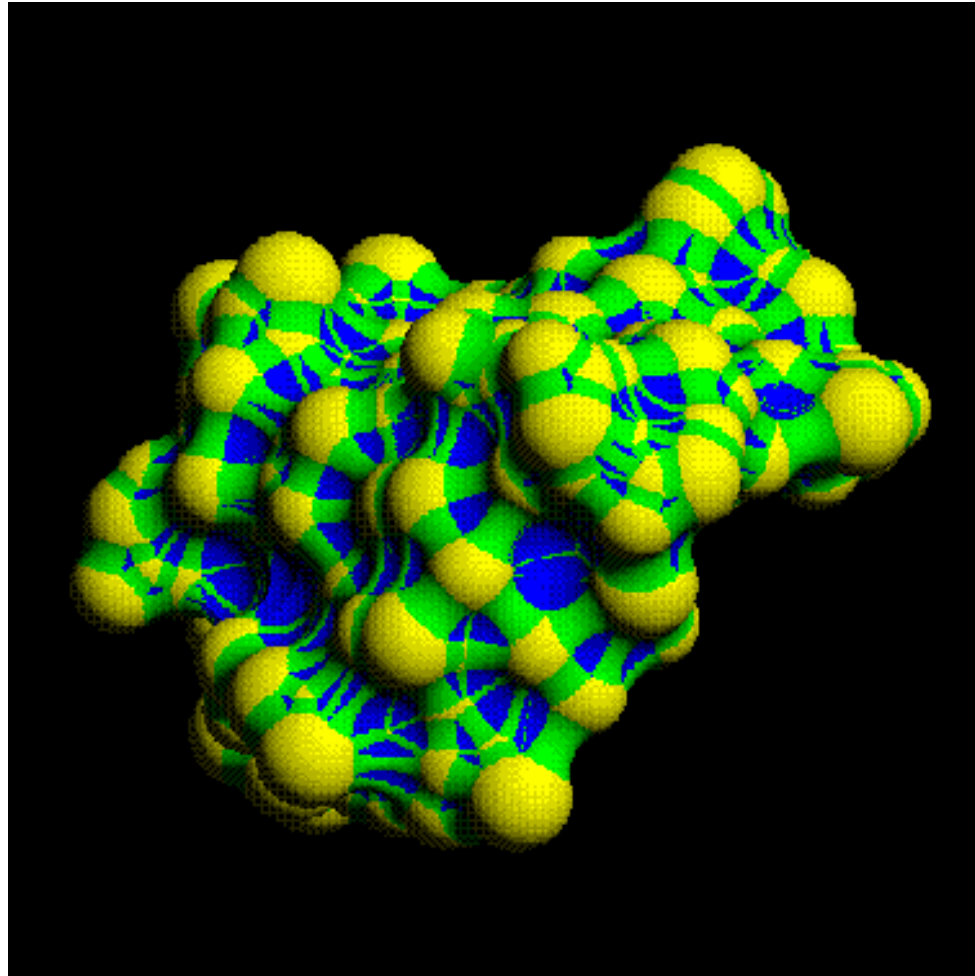
Connolly's MS algorithm

- A 'water' probe ball (1.4-1.8 Å diameter) is rolled over the van der Waals surface.
- Smooths the surface and bridges narrow 'inaccessible' crevices.

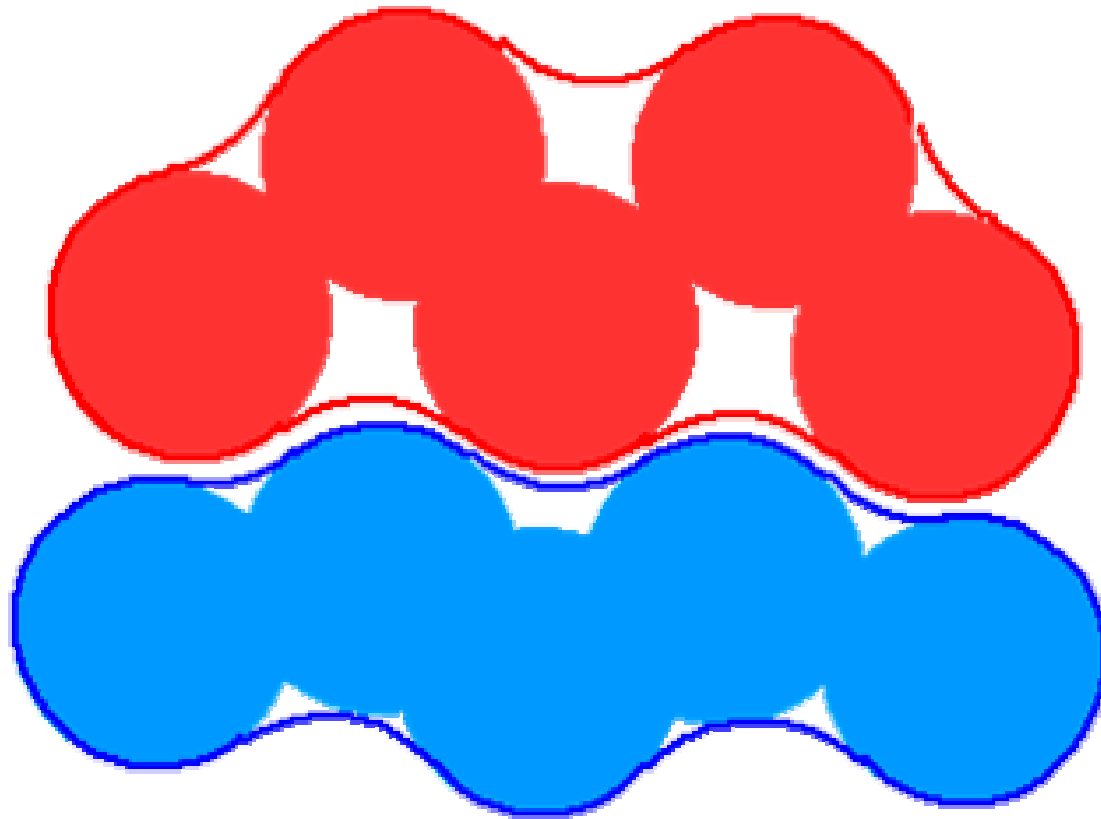
Connolly's MS algorithm - cont.

- Convex, concave and saddle patches according to the no. of contact points between the surface atoms and the probe ball.
- Outputs points+normals according to the required sampling density (e.g. 10 pts/ \AA^2).

Example - the surface of crambin



Shape Complementarity



Example : Trypsin/Trypsin inhibitor

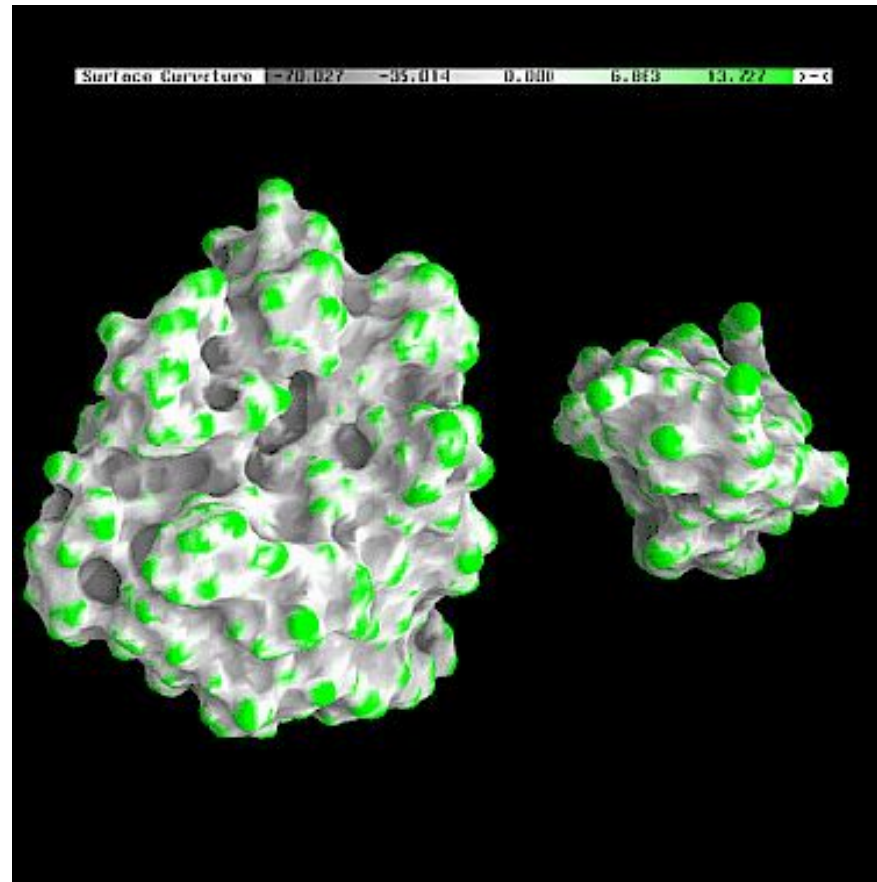


Figure from B. Honig's Labs web-site at Columbia University.

Surface complementarity calculation - discrete representations

- Connolly points + normals - dense.
- Lin et al. points - sparser.
- Knobs - holes (Connolly; Norel-Nusinov-Wolfson) - sparse.
- SPHGEN (Kuntz) - surface cavity modeling by pseudo-atom centers.

Critical points based on Connolly rep. (Lin, Wolfson, Nussinov)

- **Define a single point+normal for each patch.**
- **Convex-caps, concave-pits, saddle - belt.**

Critical point definition

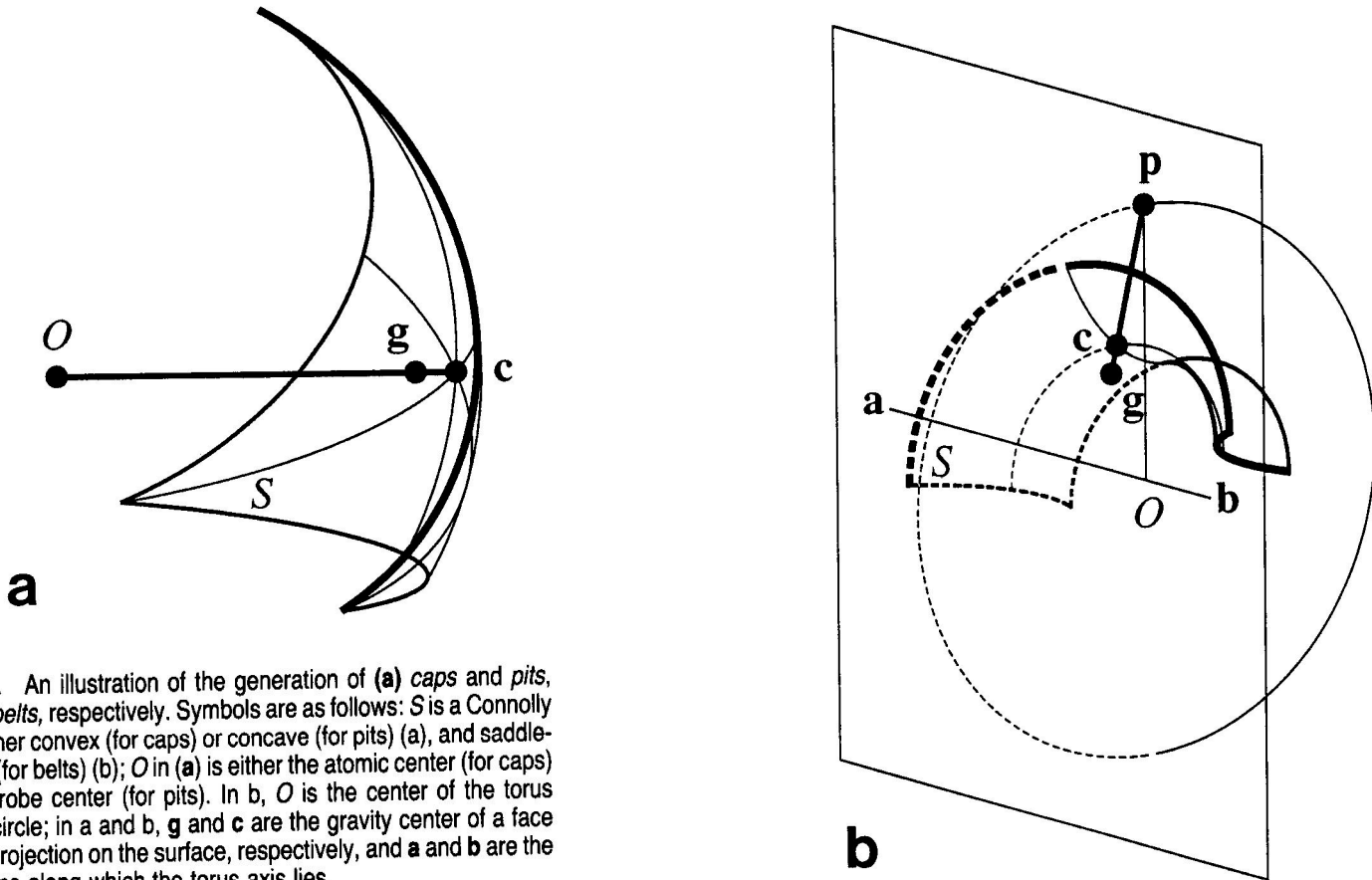
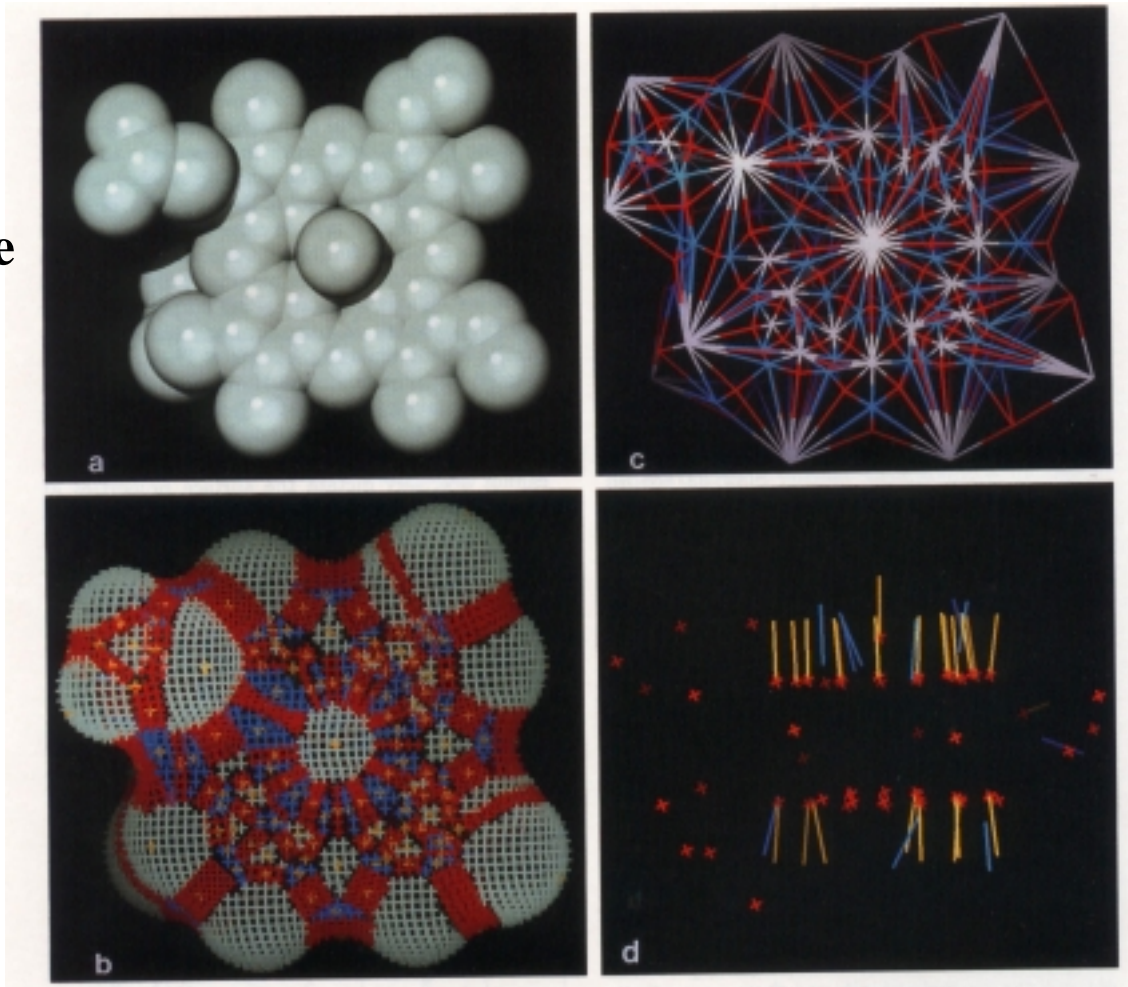


Fig. 1. An illustration of the generation of **(a) caps** and **pits**, and **(b) belts**, respectively. Symbols are as follows: S is a Connolly face, either convex (for caps) or concave (for pits) (a), and saddle-shaped (for belts) (b); O in (a) is either the atomic center (for caps) or the probe center (for pits). In b, O is the center of the torus central circle; in a and b, g and c are the gravity center of a face and its projection on the surface, respectively, and a and b are the two atoms along which the torus axis lies.

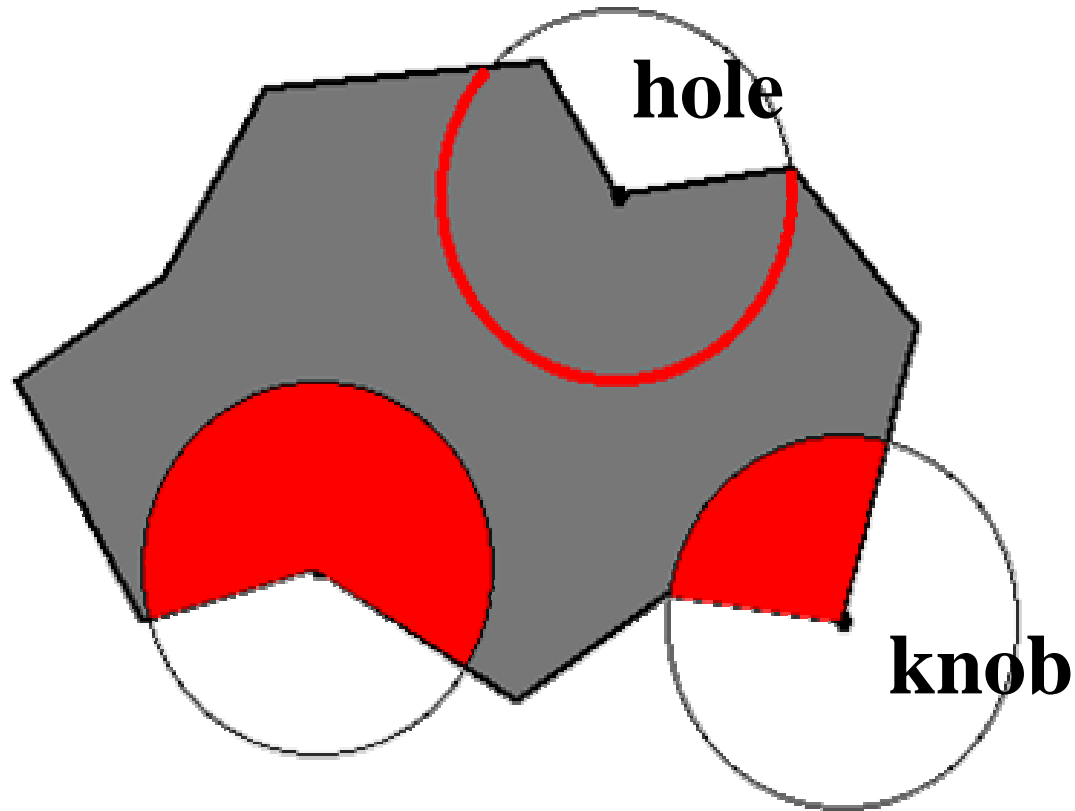
Critical point performance

heme

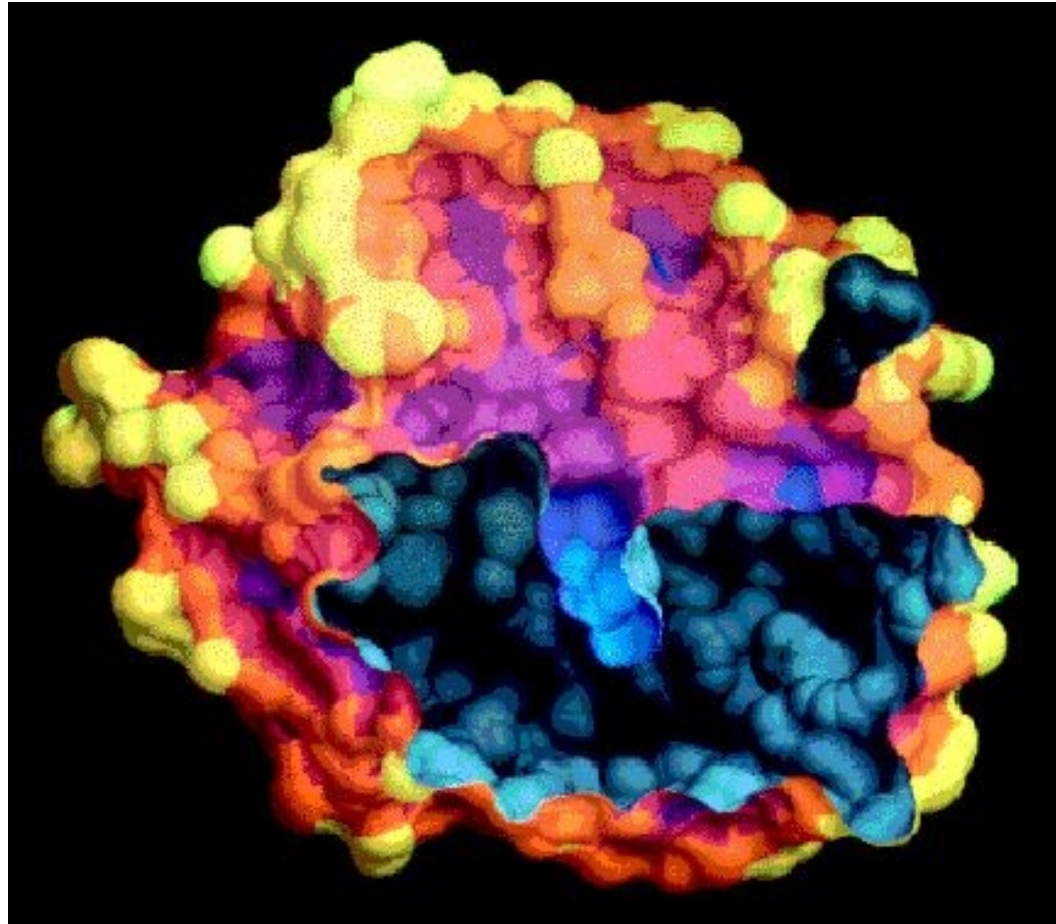


**Caps of heme
vs. pits of
myoglobin**

Solid Angle local extrema



Chymotrypsin surface colored by solid angle (yellow-convex, blue-concave)

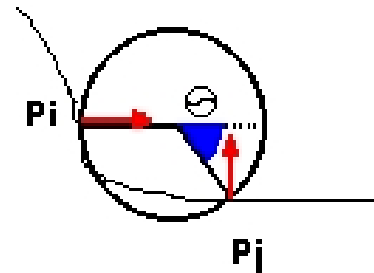


SPHGEN - complementary surface pseudo-atom calculation (Kuntz et al.)

- Attempts to model packing of spheres in a cavity (of receptor).
- The centers of the spheres model the positions of the ligand atomic centers.
- Detects both cavities and hypothesized atomic center positions.

SPHGEN – detailed (1)

- For each pair on Connolly points $\mathbf{p}_i, \mathbf{p}_j$ a sphere passing through this pair is placed such that its center is on one of the points normal.
- For each point leave only the sphere with the smallest radius. (This discards) all the spheres that penetrate the surface of the molecule.
- Leave only the spheres where $\theta < \pi/2$ (to ensure concavity).

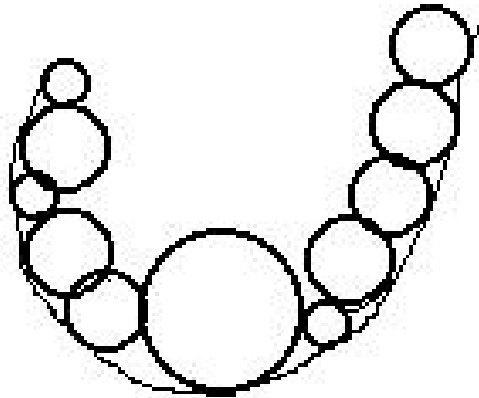


SPHGEN – detailed (2)

- For each **atom**, leave only the sphere with the maximal radius. (This step leaves only the spheres that 'touch' the surface of the atom.)
- If the points that define the sphere, \mathbf{p}_i and \mathbf{p}_j , belong to different atoms, and the distance between these atoms on the molecular sequence is less than 4 angst. - discard the sphere. (Not to capture helix grooves.)
- The remaining spheres are called pseudo-atoms.

SPHGEN – detailed (3)

- **Cluster** intersecting spheres to detect cavities.
- (Optional) Split by removing largest spheres.



Curvature calculation (Zachmann et al.)

- Fit 2nd order patches to the Molecular Surface (possible at different resolutions).
- Compute the mean and Gaussian curvatures from the IInd fundamental form matrix.
- Compute the principal curvatures of the quadratic patch.

Hydrogen bond complementarity modelling (Lengauer et al.)

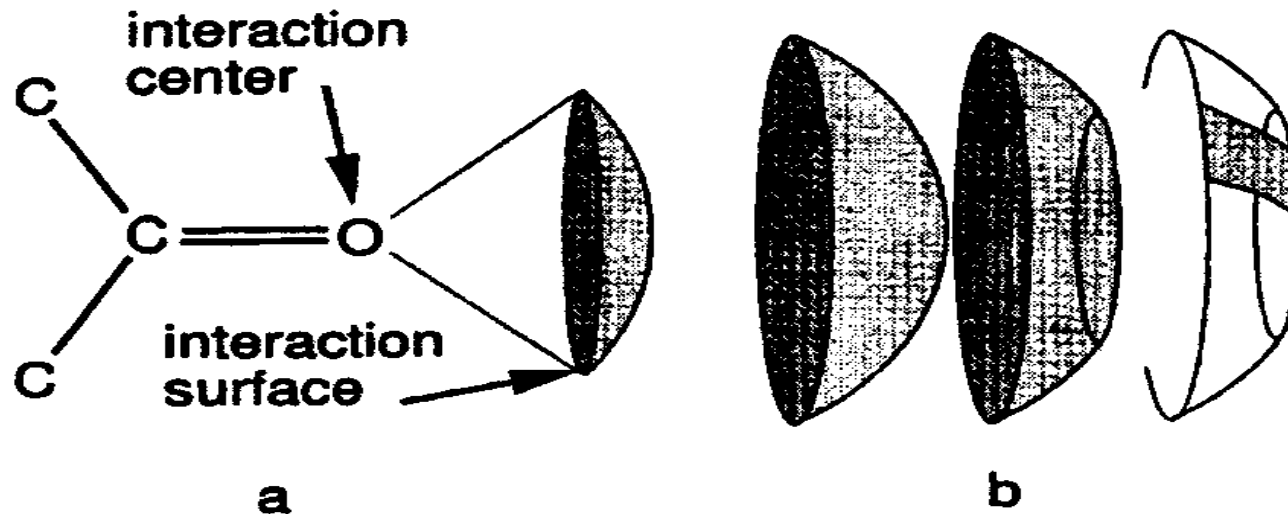
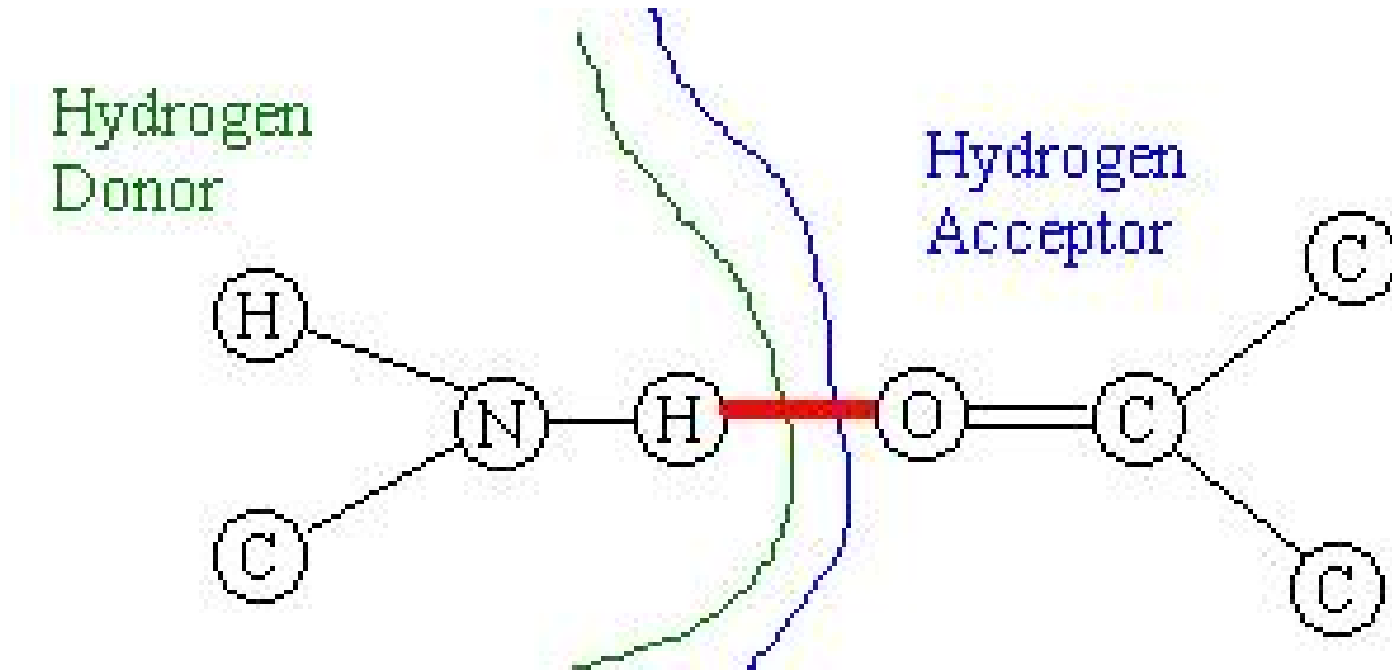


Figure 1. Interaction geometries. a, Interaction center and surface pertained to a carbonyl group. b, Three of the four different types of interaction surfaces: cones, capped cones and spherical rectangles.

Hydrogen bond –reminder



Geometric constraints :

1. Distance.
2. Directionality.

Hydrogen bond complementarity

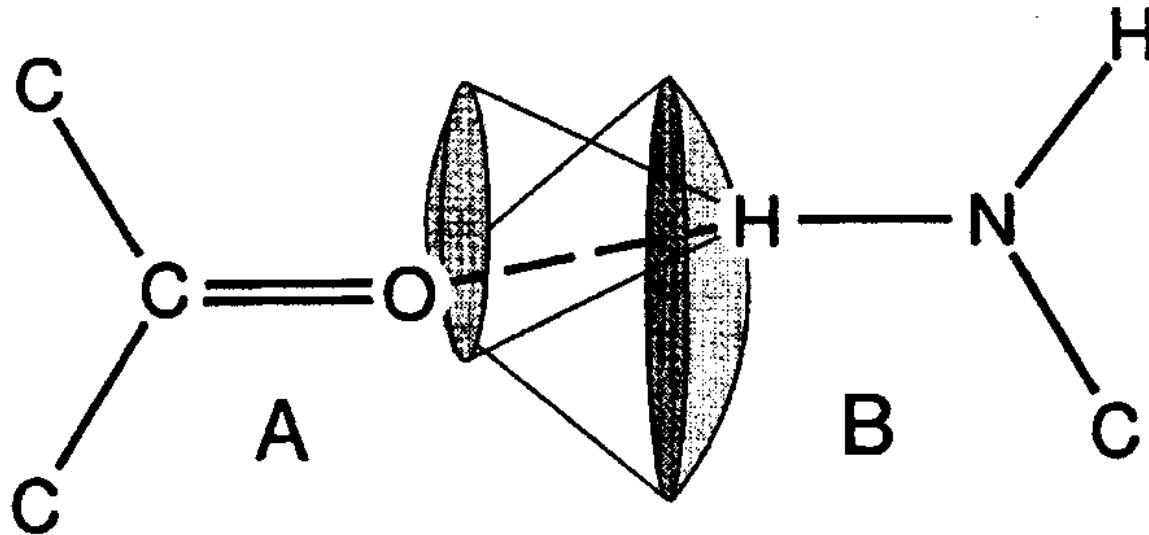


Figure 2. Condition for the formation of interactions: a hydrogen bond between the carbonyl oxygen and the nitrogen. The interaction centers are the oxygen and the hydrogen atom forming the hydrogen bond. They have to fall mutually on the surrounding interaction surfaces.