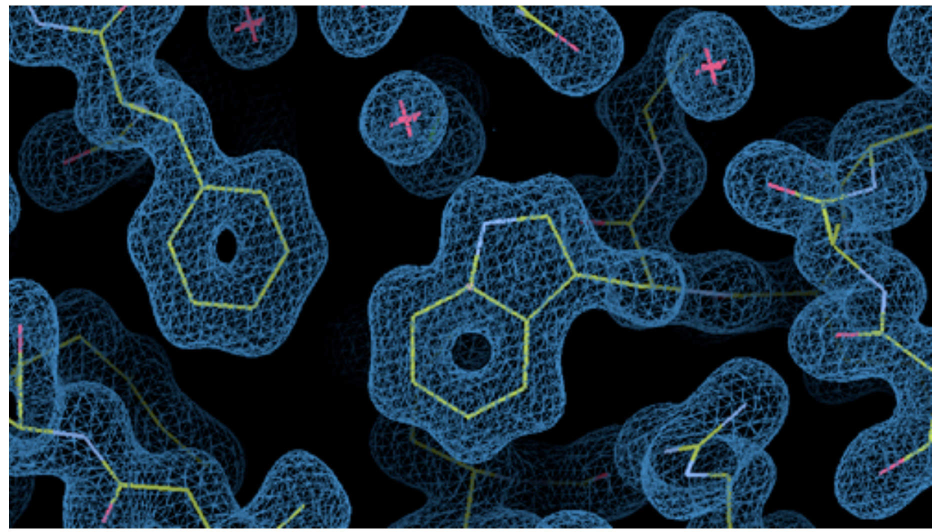
Bioinformatics 2: Lecture 10

- Waters.
- Surfaces.
- Voids.

10.1 Modeling waters

Crystallographic waters

- **Waters** are identified in crystal structures by calculating difference density -- called a Fo-Fc map. Unexplained difference density that is small and near other atoms is usually assumed to be water. It could also be sodium or, chloride, or other similarly dense atoms.
- Waters may be **conserved** across homologous proteins.
- Waters can be essential for protein **function**.



PDB format
water molecules

```
HETATM 1829  O   HOH     1      10.795  56.972   8.246  1.00  6.52      1CSK1904
HETATM 1830  O   HOH     2      51.191  60.117  23.250  1.00 25.95      1CSK1905
HETATM 1831  O   HOH     3      26.169  62.394  20.652  1.00 27.73      1CSK1906
HETATM 1832  O   HOH     4       9.508  75.271  29.055  1.00 17.49      1CSK1907
HETATM 1833  O   HOH     5      53.620  53.827  11.102  1.00 25.89      1CSK1908
HETATM 1834  O   HOH     6      46.106  58.319  21.139  1.00 23.45      1CSK1909
HETATM 1835  O   HOH     7      48.126  63.603  23.395  1.00 28.27      1CSK1910
HETATM 1836  O   HOH     8       7.579  60.532   8.324  1.00 22.14      1CSK1911
```

occupancy B-value

Modeling waters

- When to model waters
  - When water is part of the binding site
  - When water is involved in the enzyme reaction

- How to model waters
  - Add waters where voids and H-bond partners exist.
  - Add automatically.
  - Energy minimize. Run molecular dynamics.

Exercise 10.1

- Add waters to a structure that has none.
- Make a hydration layer
- “Freeze dry” surface waters
- Minimize. Dynamics.
- Identify fixed waters.

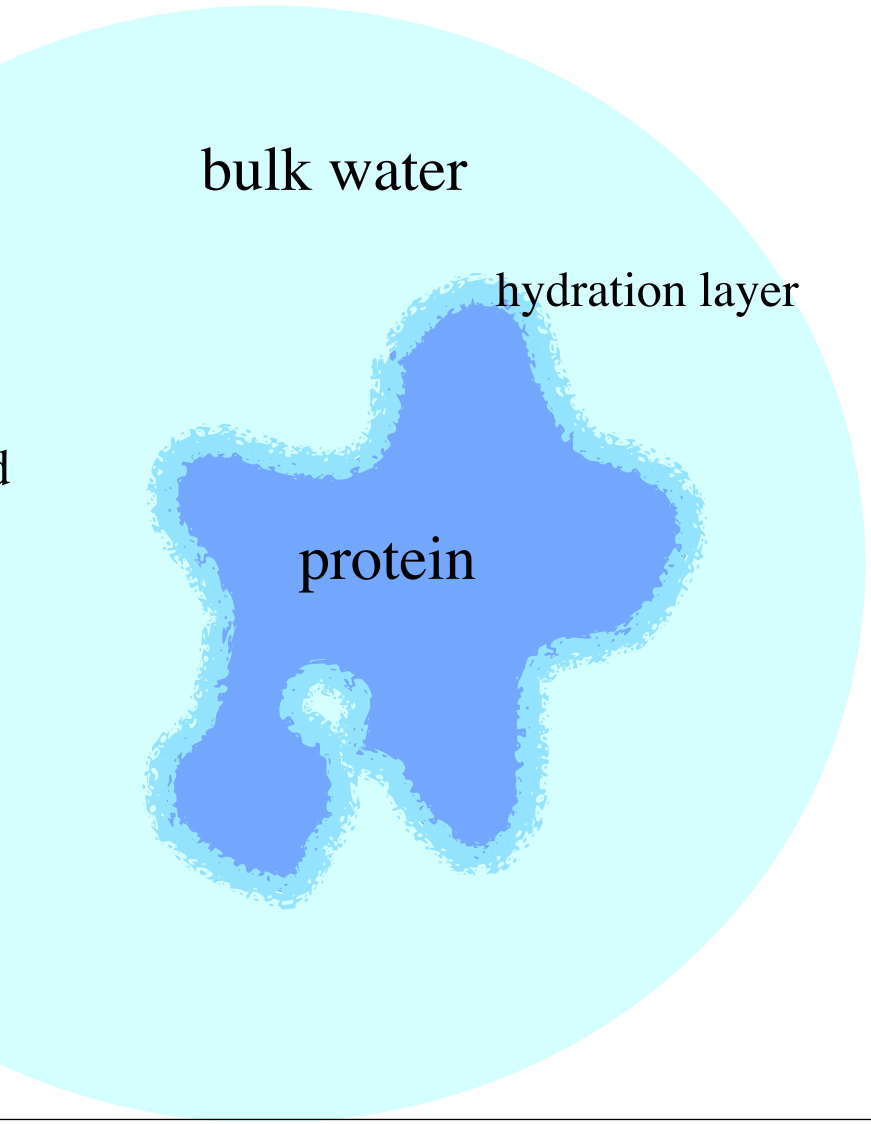
10.2 Surfaces

Molecular surface

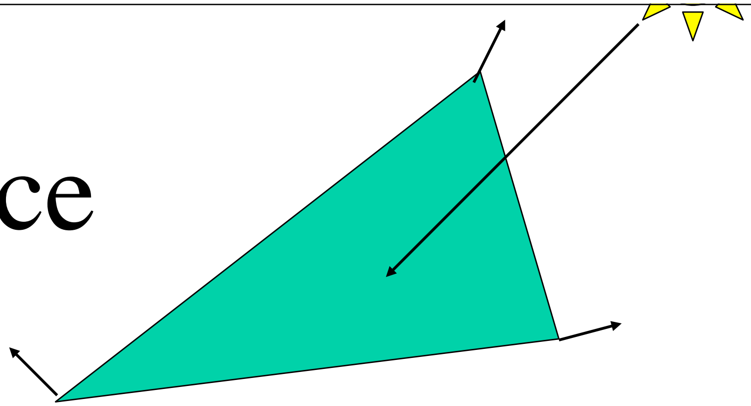
A molecular surface is the border or interface between a molecule and its environment: where interesting things happen!

Water that sits on the surface behaves differently than water that is surrounded by water. Therefore, surfaces can be used to model *solvation*.

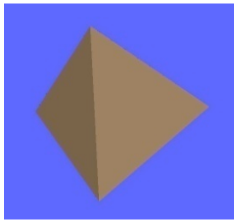
Surfaces properties:
• size/area
• electrostatic properties
• shape properties (convex, concave)



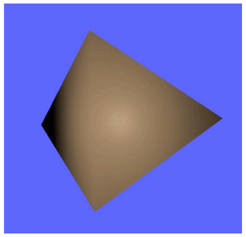
Rendering a surface



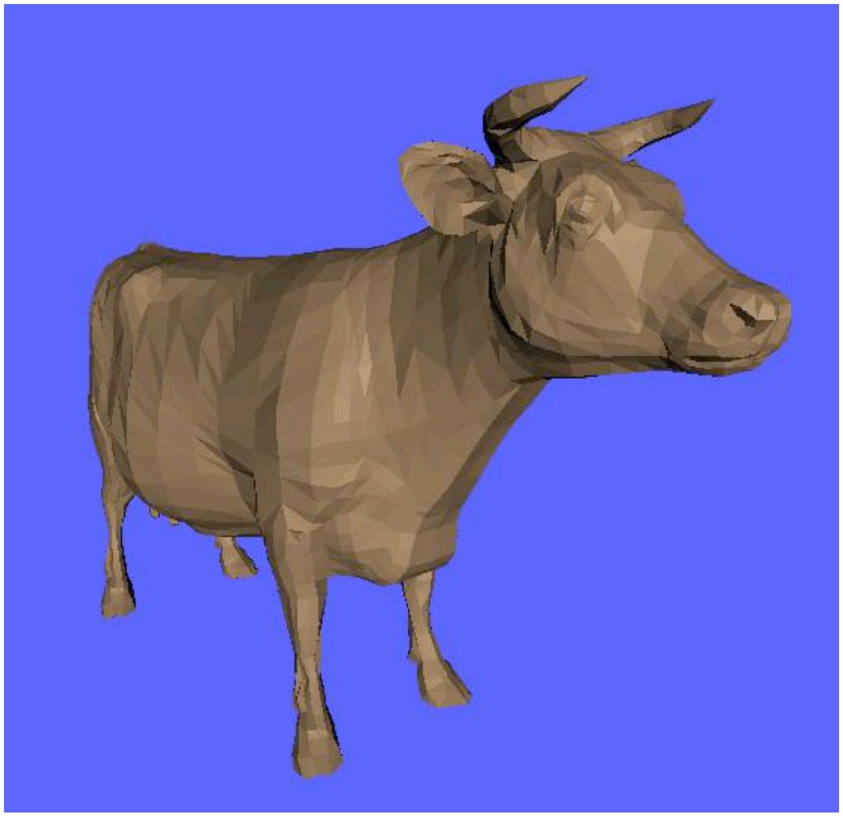
- *A surface of any shape may be represented by **triangles***, that is, 3 sets of xyz coordinates, one for each vertex.



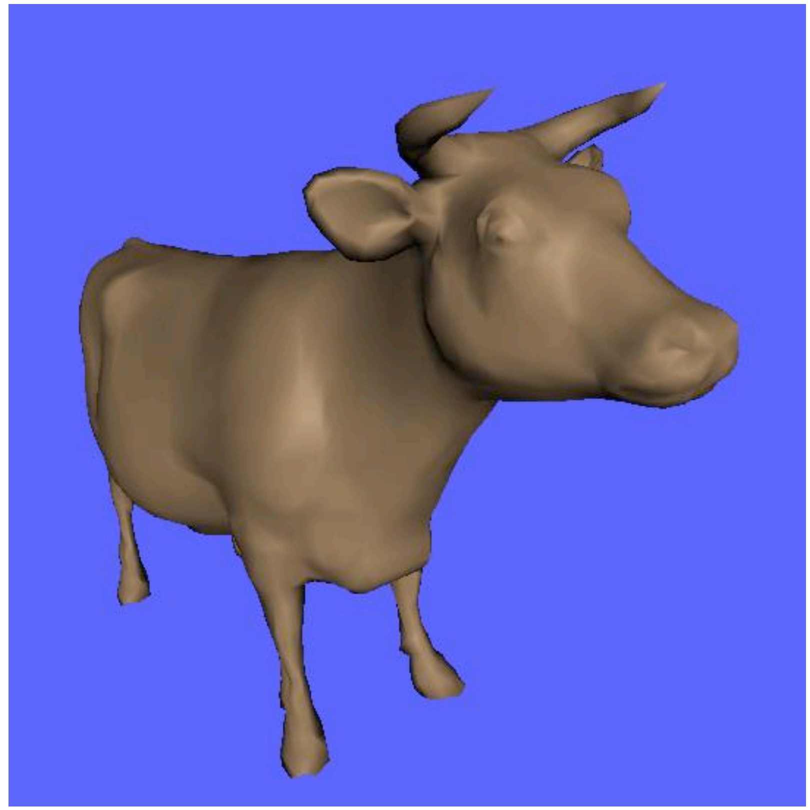
- Triangles linked edge to edge form a continuous surface (called *tesselation or tiling*).
- Each pixel in the triangle is assigned a **brightness** according to the angle between the triangle and the light source.
- **Phong shading** may be applied to simulate *curvature*.



renderings



A tesselated cow.



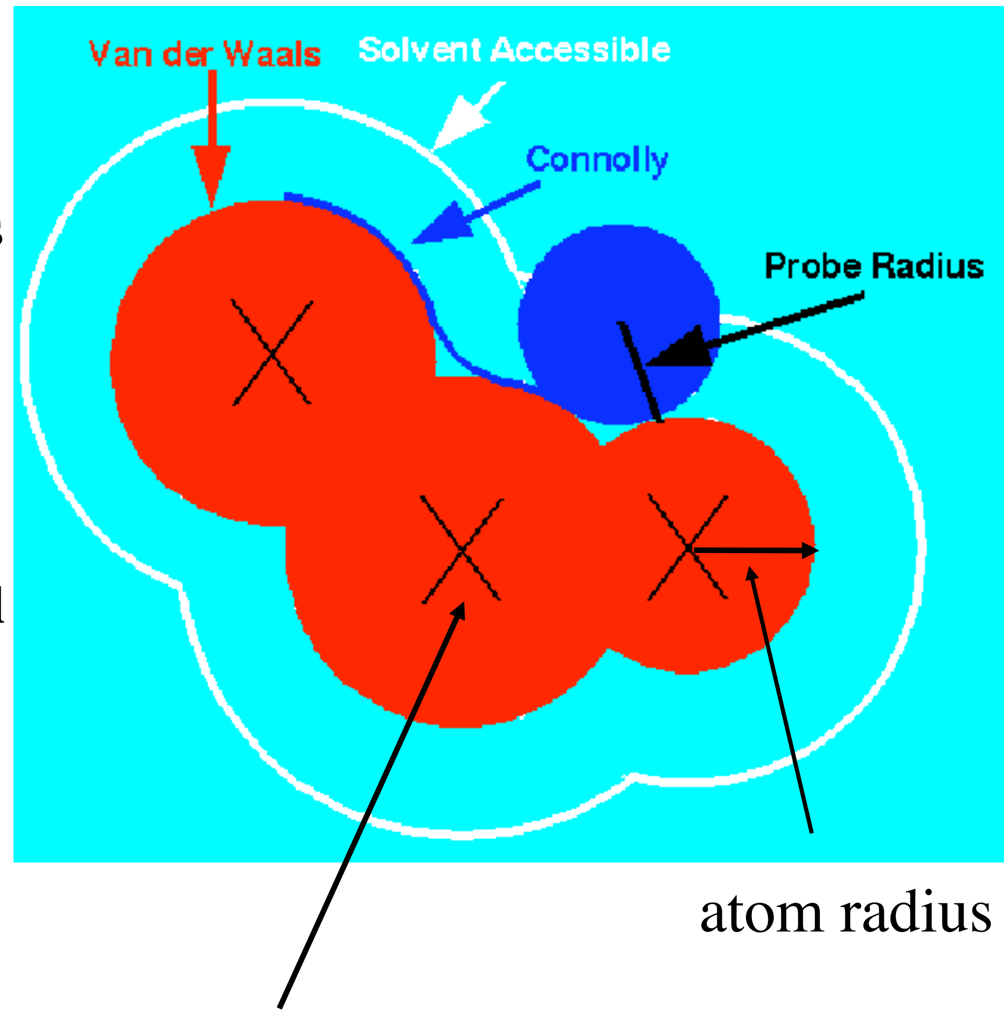
Same tesselation. Phong-shading added.

Solvent probe: the Connolly surface

Roll a probe sphere over the molecule:

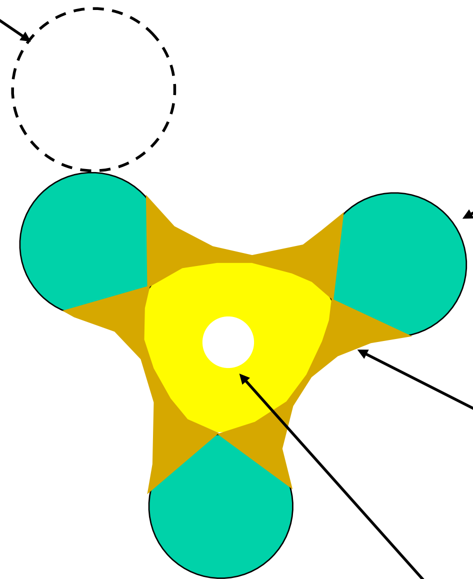
•The center of the sphere traces out the **Solvent Accessible Surface (SAS).**

•Everywhere the sphere touches (including empty space) is the **Solvent Excluded (or "Connolly") Surface (SES).**



Three types of Connolly surface

rolling probe sphere



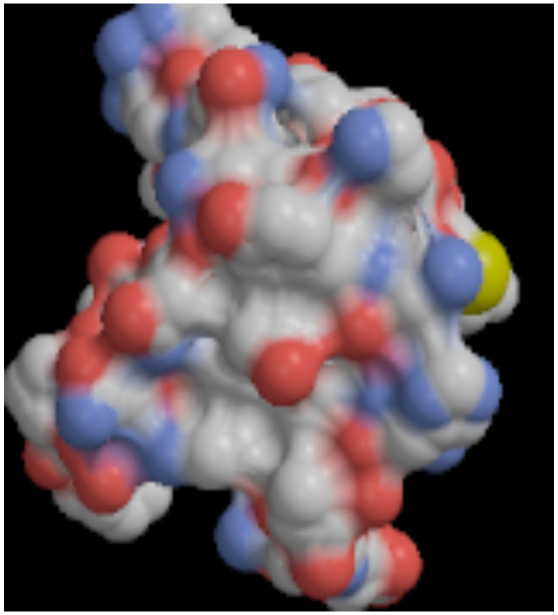
Green: **contact surface** when probe touches one atom

Brown: **toroidal surface** when probe touches two atoms.

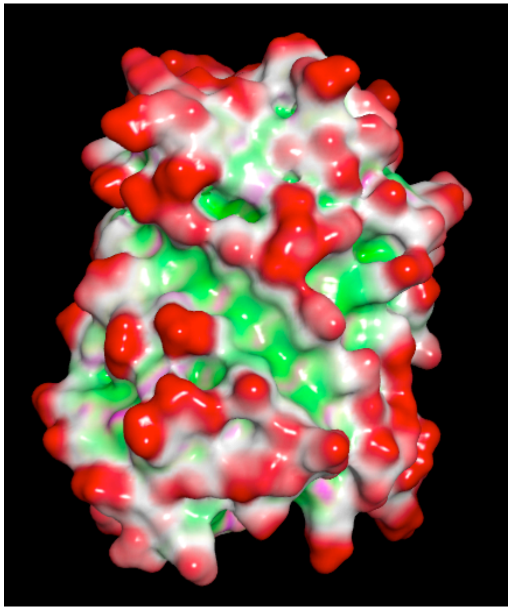
Yellow: **reentrant surface** when probe touches three or more atoms.

(may have a hole in the middle)

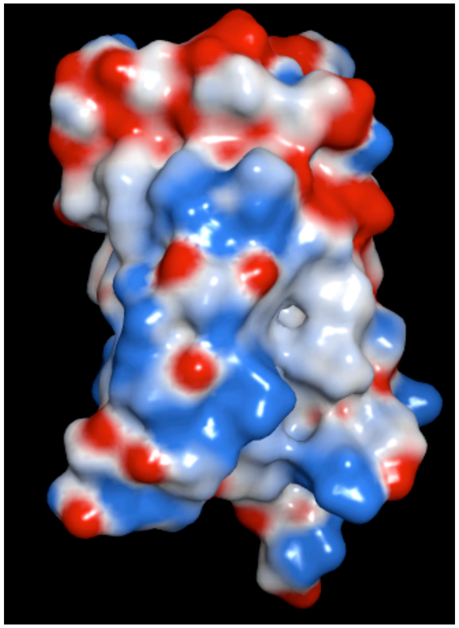
Surface coloring representations



atom color



surface curvature



electrostatic potential

Exercise 10.2

- Add a molecular surface to the protein in Ex. 10.1
- Use “pocket” coloring.
-

How do surfaces interact?

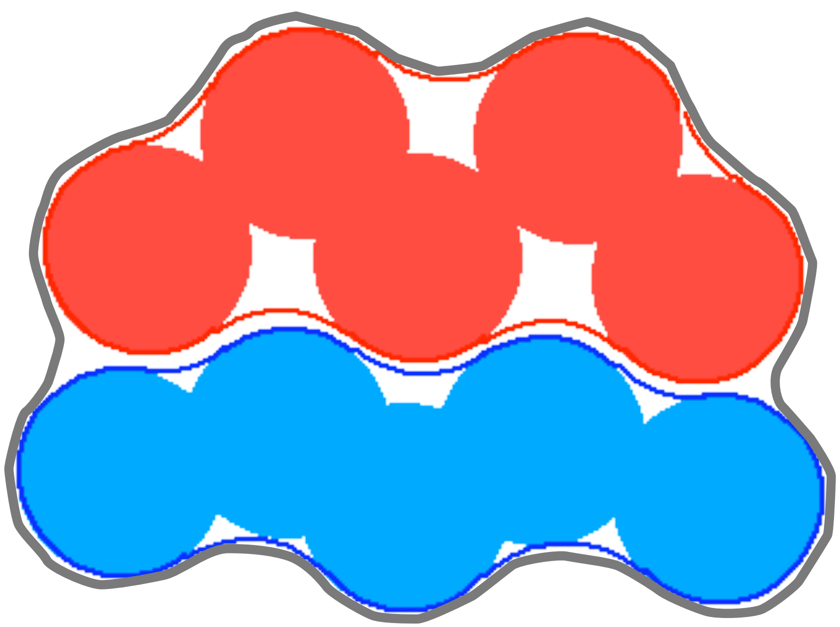
Molecular surfaces dictate the function of a molecule, whether it is signaling protein, an enzyme, a channel, an integral membrane protein, ...

Proteins interact by

•Shape complementarity

•Charge complementarity

Solvent excluded surface complementarity.



Complementary surfaces leave relatively little unfilled (void) space.

White space within colored outlines are **solvent excluded** spaces in the *monomer*.

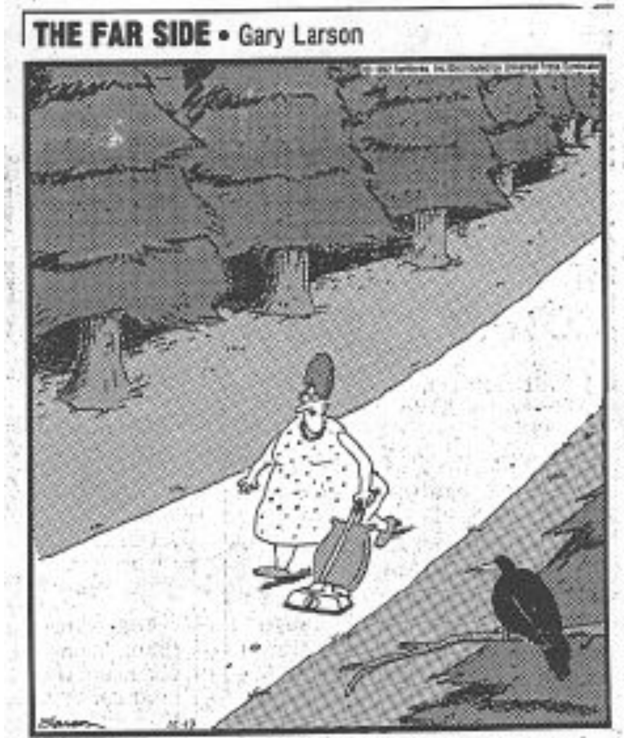
White space in grey outline is solvent excluded in the *dimer*.

No addition solvent excluded space means tight binding.

10.3 Voids

Nature abhors a vacuum

no, not this kind...

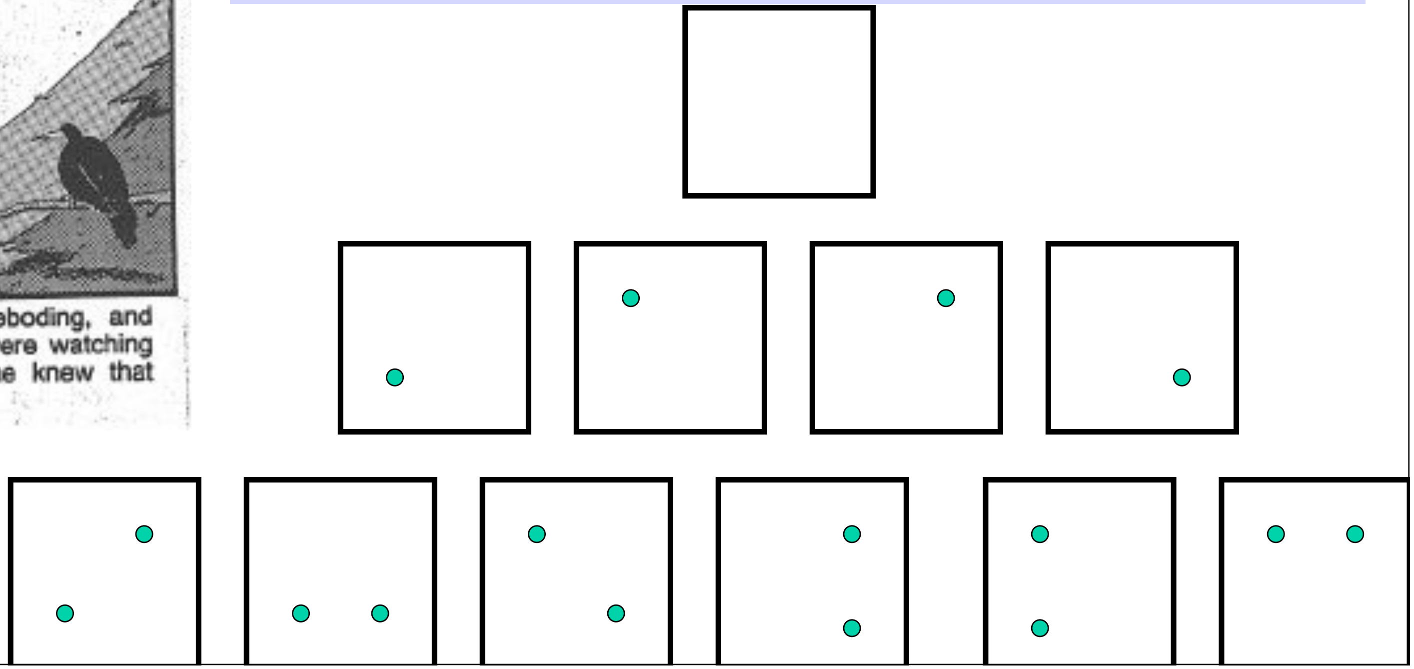


The woods were dark and foreboding, and Alice sensed that sinister eyes were watching her every step. Worst of all, she knew that Nature abhorred a vacuum.

There is only one way to make space empty, but many ways to fill it.

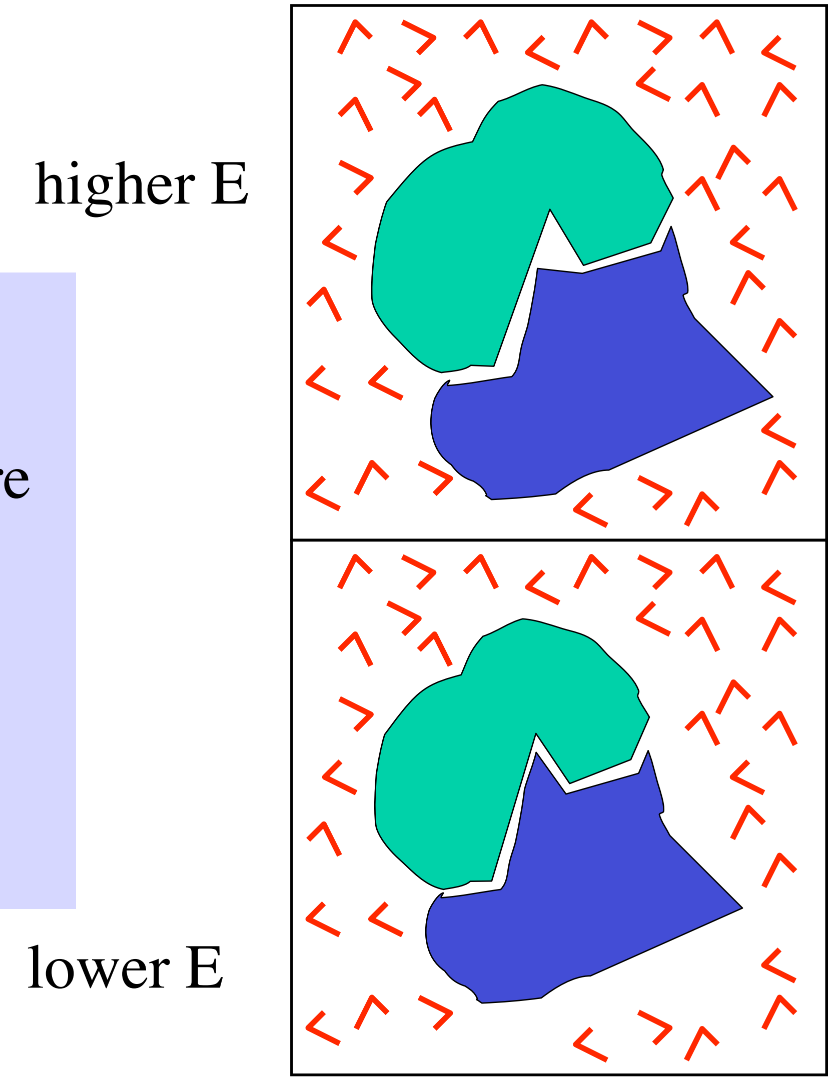
The entropy is larger if *number of different states available to the system is larger*.

Lower entropy implies higher free energy (unfavorable).



Better fit, less wasted space, lower energy.

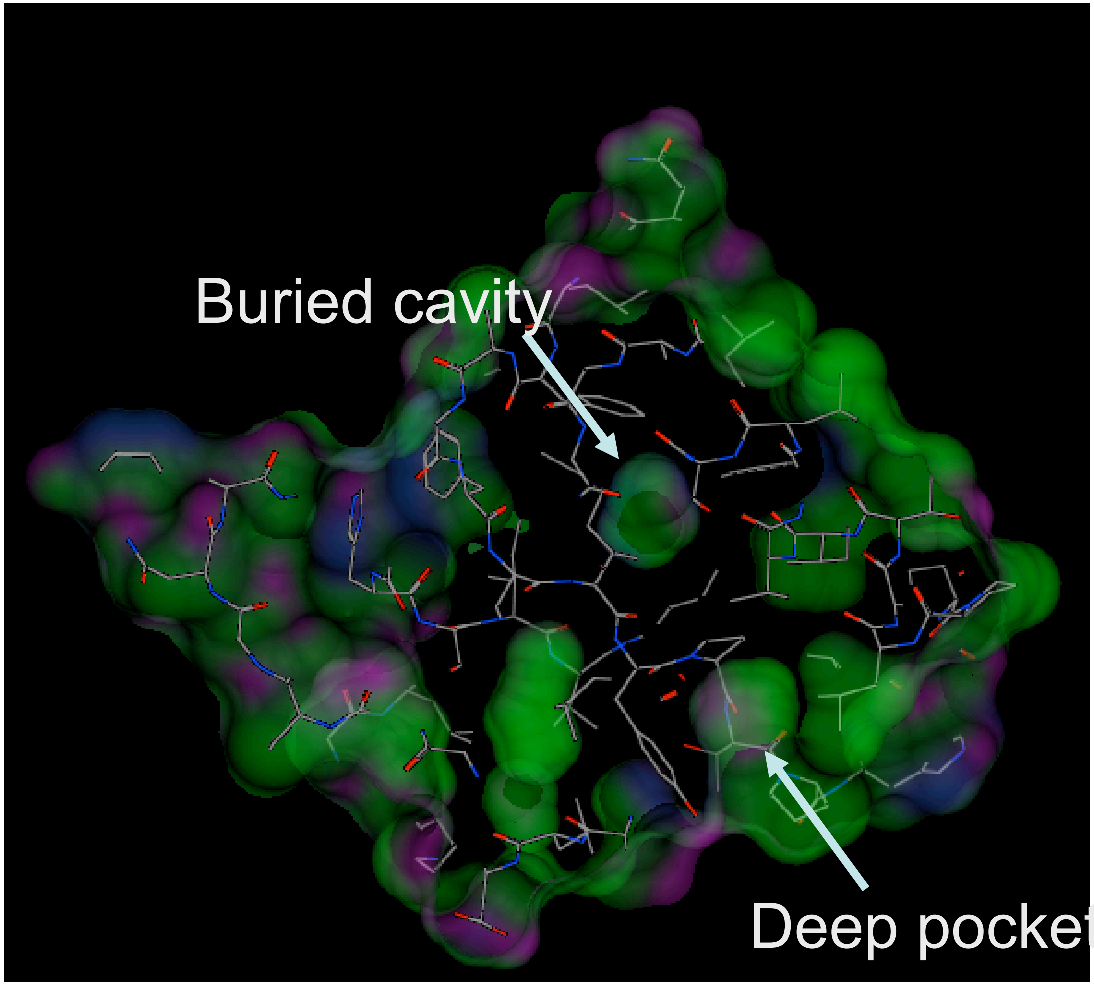
If we compare two surface-surface interactions, all else being equal, the one with more void spaces has a higher free energy, and is therefore less favorable.
The one that fills space has a lower energy.



Finding Voids

- Compute | Surfaces & Maps
  - Molecular surface, receptor atoms, near receptor atoms
- cntrl-G (Window->Graphic objects)
  - Set transparency to allow you to see the atoms through the front surface
- When you have located a buried cavity, show all atoms, then select the atoms around the cavity.

Voids



Filling voids

- Fill by rotating side chains
  - Compute | Biopolymer | Rotamer explorer
    - Find side chains surrounding the void. Rotate them and recalculate the surface.
- Fill by adding water
  - Does the cavity have polar sidechains, especially charged groups?
    - Add a water and energy minimize it.
- Leave it alone.
  - Empty cavities occur in proteins.
    - May be important for enzyme activity, especially at low temperatures. (See Paredes et al 2011)

Exercise 10.3

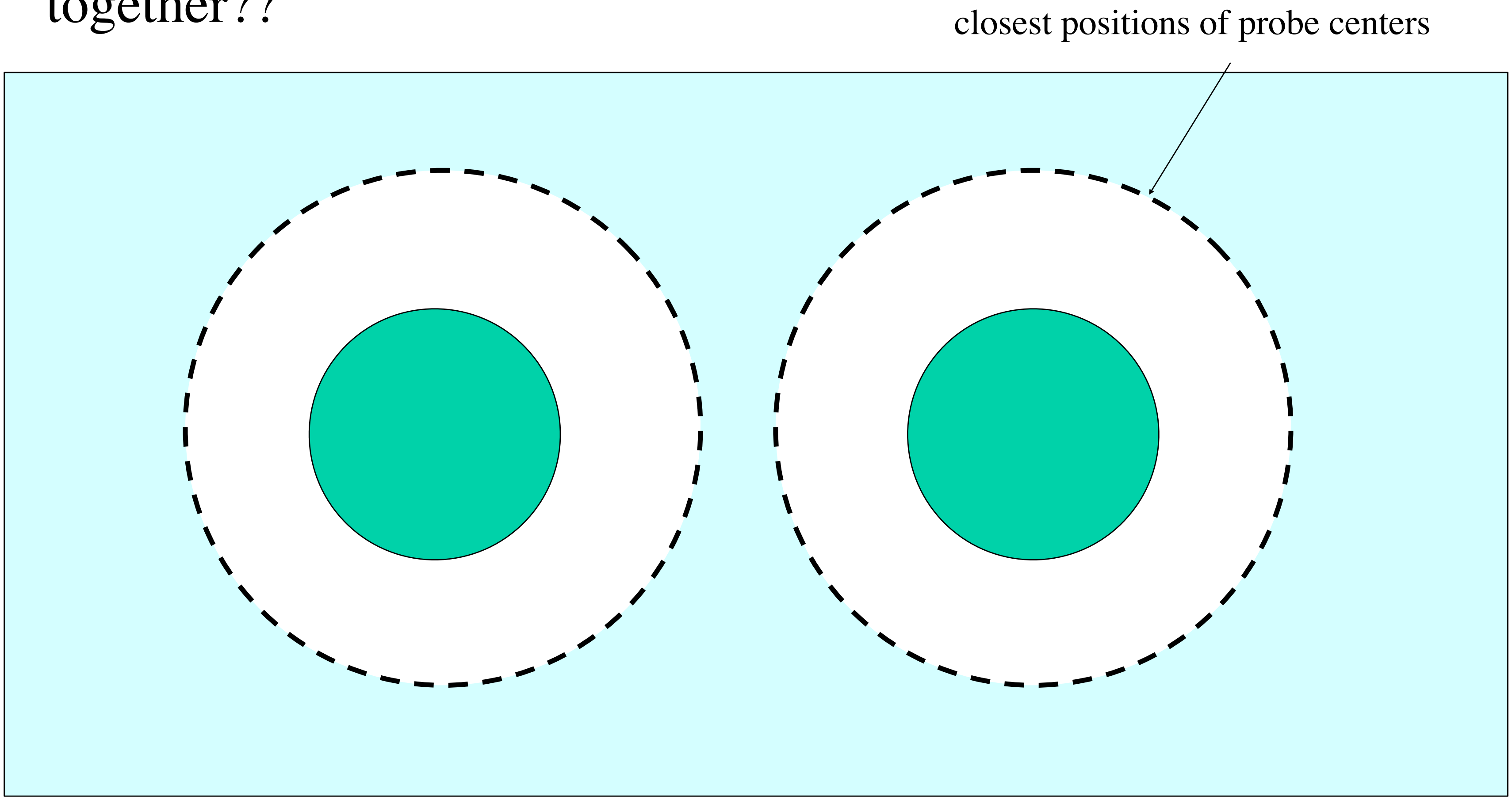
- Find buried cavities in molecule from Ex 10.2
- Add waters to cavities.

Supplementary

- Comparison of solvent excluded surface area and hydration energy for a simple two-atom system. (next five slides)
- Note how SES models the hydrophobic effect.
- Reasons: waters that are trapped between hydrophobic atoms have low entropy (high energy).

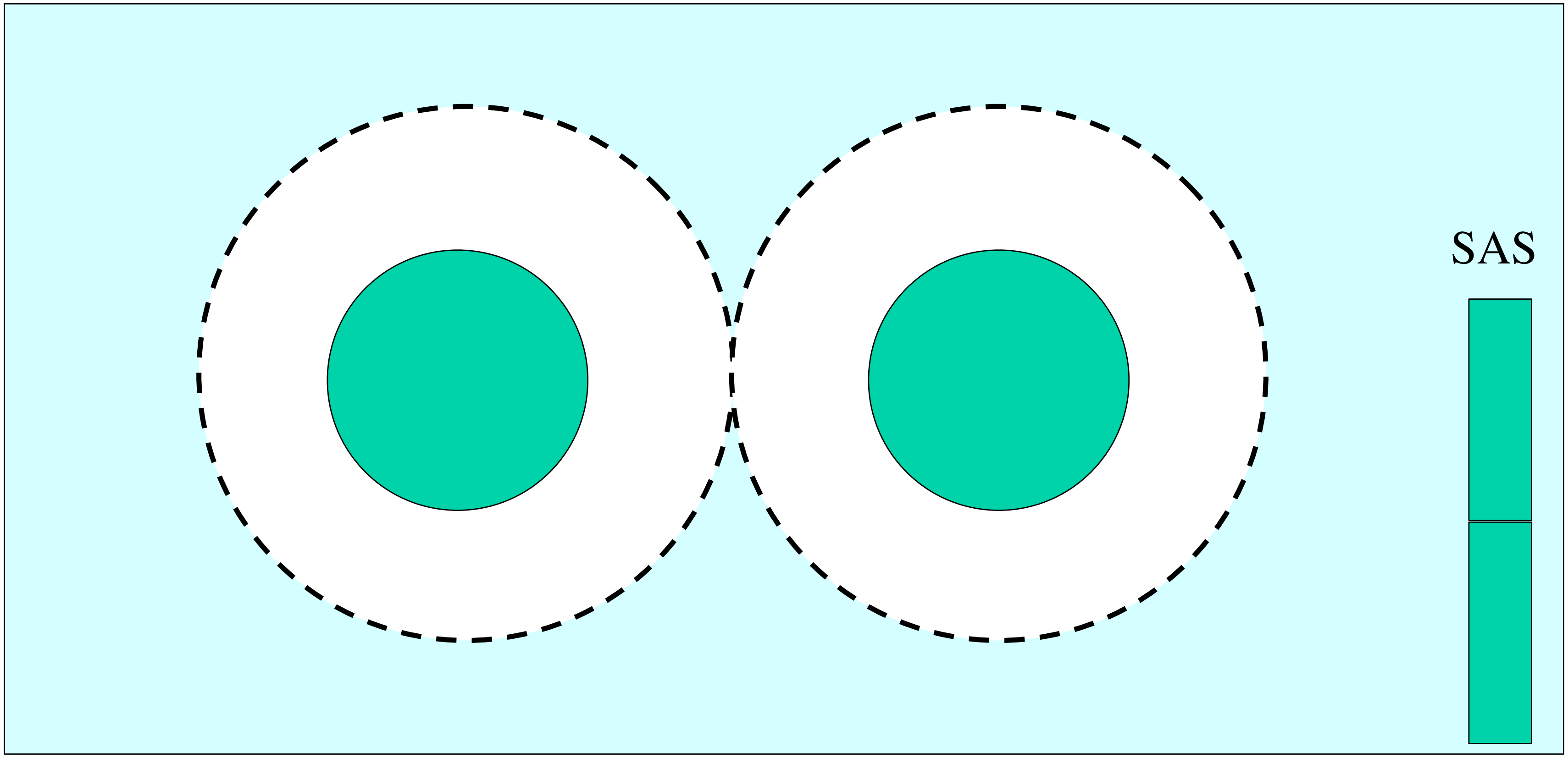
The Hydrophobic Effect

What happens to the **surface** as two hydrophobic spheres come together??



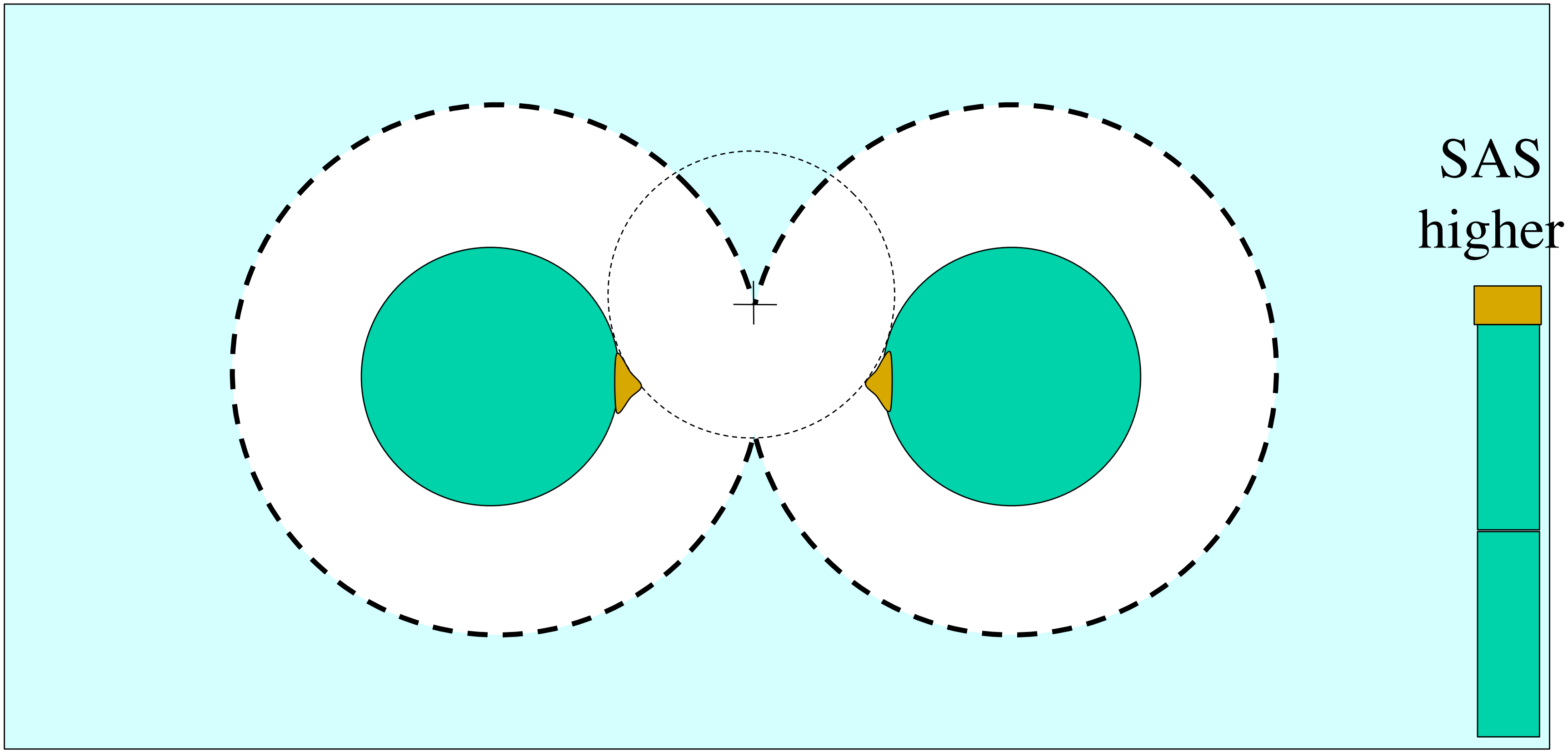
The Hydrophobic Effect

White area is excluded volume. Water can't go closer than one radius (1.4 Å).



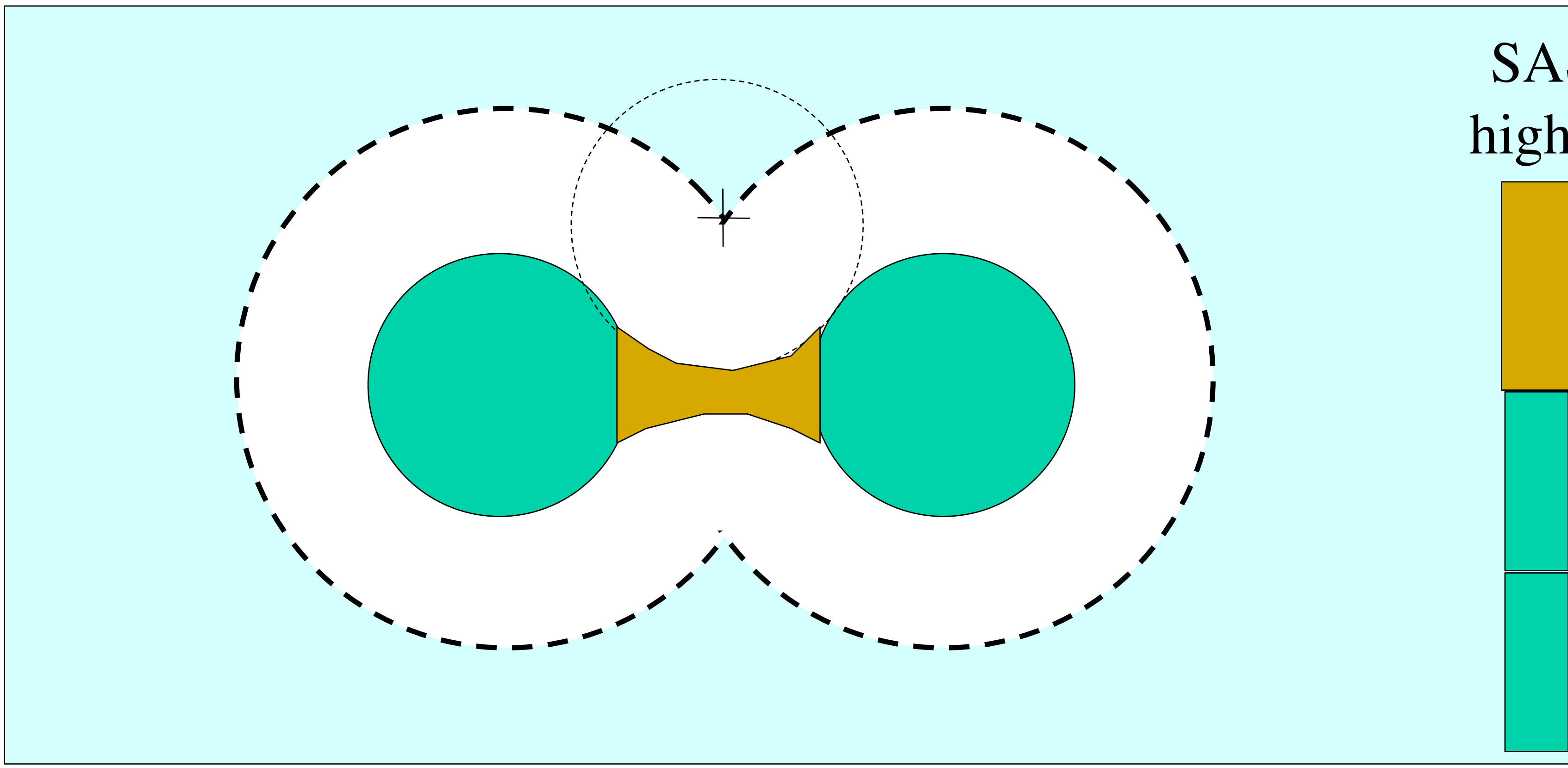
The Hydrophobic Effect

First, SAS (green) is increased by new "toroidal" surface (brown).



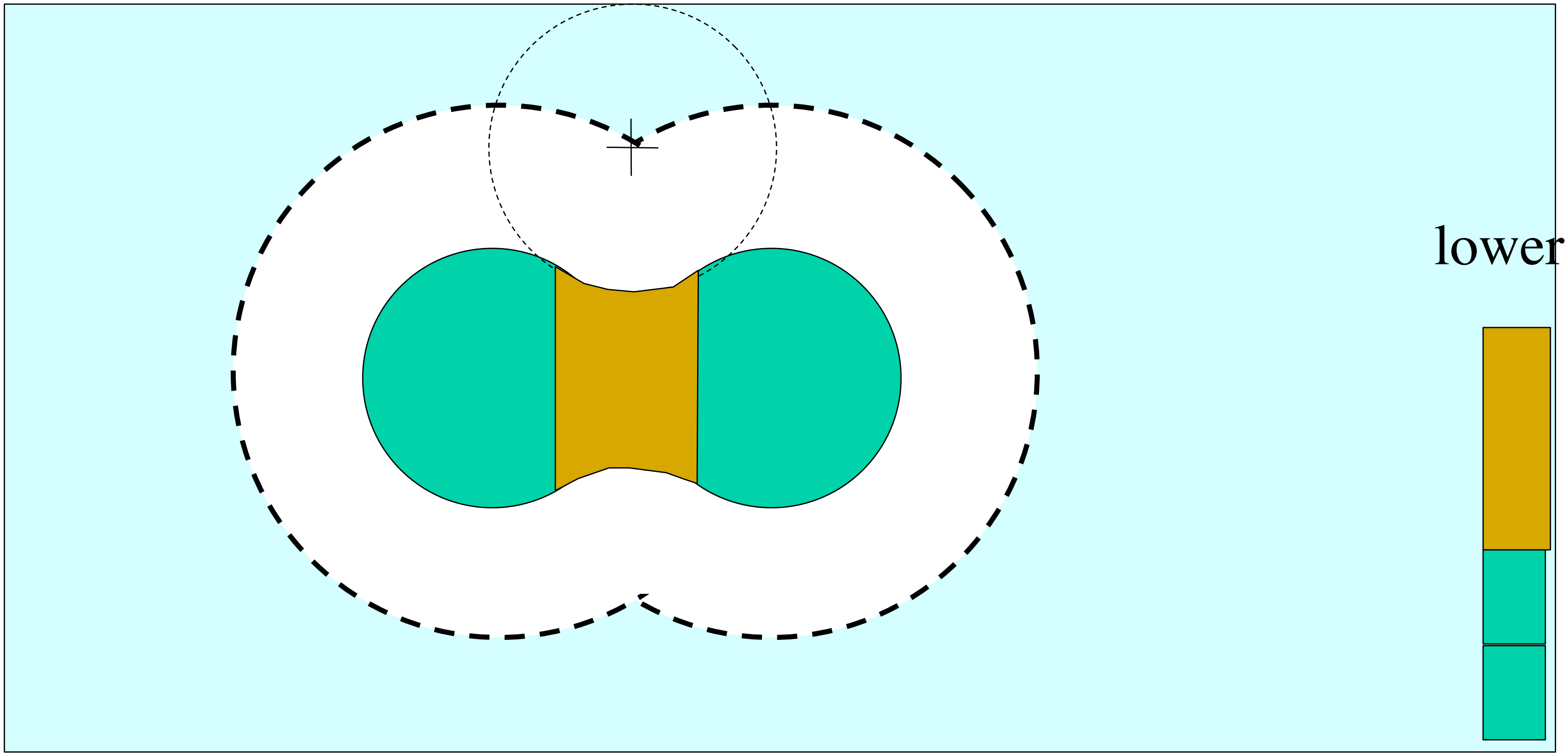
The Hydrophobic Effect

Toroidal surface (brown) grows faster than atom surface is lost.
SAS goes up.



The Hydrophobic Effect

At short distance, toroidal surface stops growing, atom surface shrinks faster.

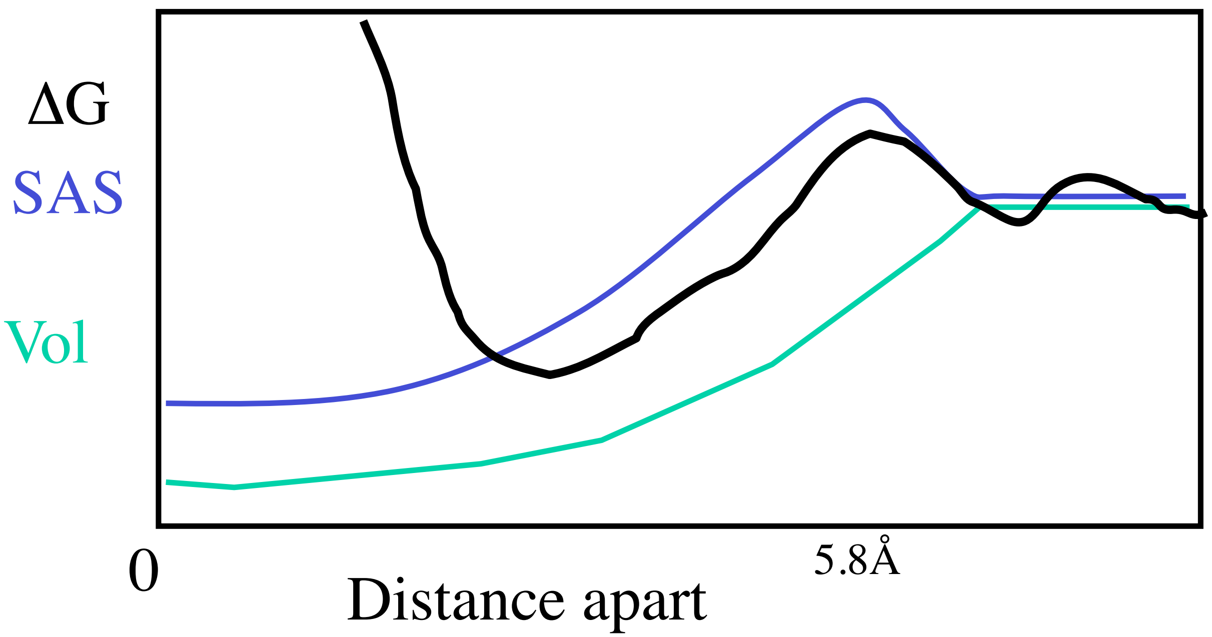


Is there an energy barrier to hydrophobic collapse? (yes)

black: ΔG calculations using explicit waters

blue: SAS

green: excluded volume



Solvation energy parallels SES, not excluded volume.
Thus hydrophobic surface area is important for understanding hydrophobic effect and hydrophobic interaction.