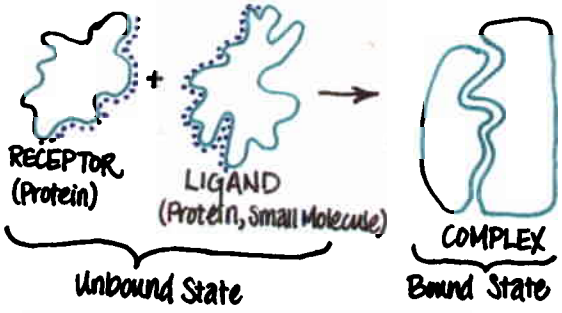
16 FEB 06

LECTURE 4: BINDING & Ddocking

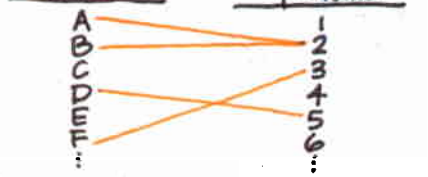
END OF PREVIOUS LECTURE

- Dahiyat & Mayo Science 278:82-87 (1997)
  - Known protein Zif-268
  - At each position allowed the actual & other compatible amino acids each in multiple rotomers
  - Sequence complexity $(S)^N \sim 1.9 \times 10^{37}$
  - Structural complexity $(M)^N \sim 1.1 \times 10^{62}$
  - DEE → 90 CPU hours → Global Optimum
  - Synthesize corresponding protein & characterized
    - adopted the same fold as the natural sequence
    - had cooperative transition



Prediction of Bound State from Unbound

1) Understanding
2) Predict binding specificity & partnering



3) Drug discovery & drug design

virtual Screening

Simplify to Rigid Binding

3 trans +3rot 3 trans +3rot

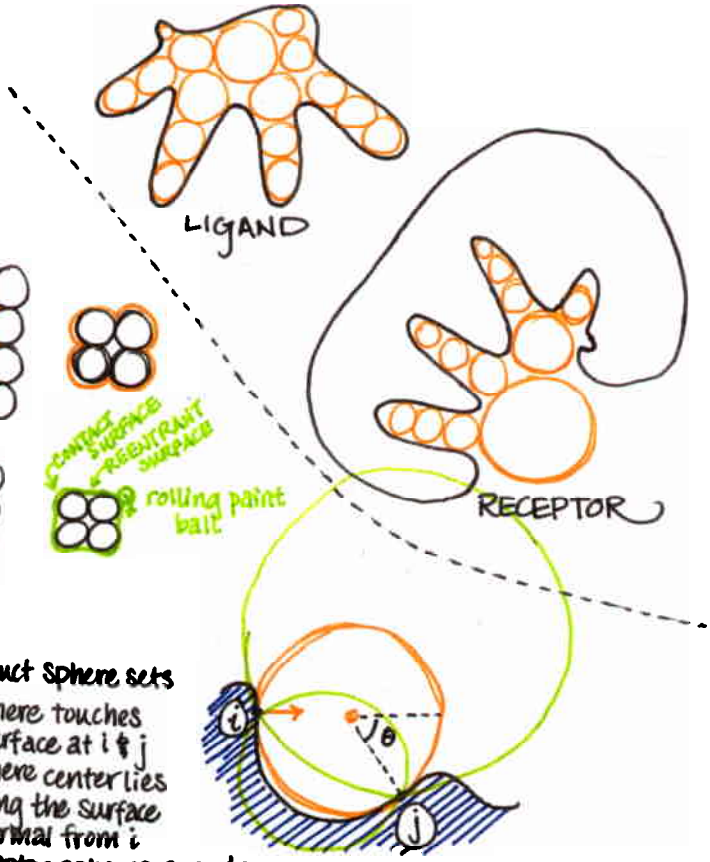
→ 6 dof

0.1 Å grid across 20 Å (~ size of a molecule) → 200 grid pts per dimension
→ 1.9×10^{14} poses

- ID Kuntz et al J. Mol Biol 161:269-288 (1982)

3 Steps:

1) Representation - useful abstraction
   Ligand - (positive) - spheres
   Receptor - (negative) - spheres
2) Matching
   - recognize similar features in ligand● and receptor⊖
3) Fitting



DETAILS

Construct Sphere sets

1. Sphere touches surface at i & j
2. Sphere center lies along the surface normal from i
3. Receptor spheres are drawn "outside" surface; ligand spheres "inside"

Then produce reduced representation

- at each point, there are (n-1) spheres
- retain the smallest - removing spheres that cross surface
- preference for $\theta < 90°$
- keep only one sphere per atom
- largest from contact points on receptor (convex)
- largest from reentrant pts on ligand (concave)

First Result:

overlapping receptor spheres, tend to represent binding sites (known)

Sphere pattern in ligand ↔ sphere pattern in receptor