Protein-Ligand Docking Methods

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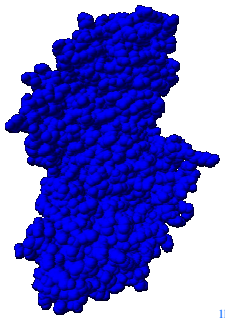
Princeton University
CS597A, Fall 2005

Review

Goal:
- Given a protein structure, predict its ligand bindings

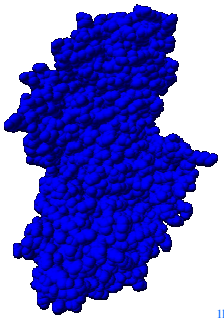
Applications:
- Function prediction
- Drug discovery
- etc.



1hld

Review

Questions:
- Where will the ligand bind?
- Which ligand will bind?
- How will the ligand bind?
- When?
- Why?
- etc.



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Protein-Ligand Docking

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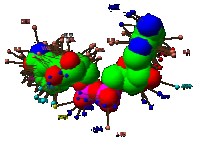

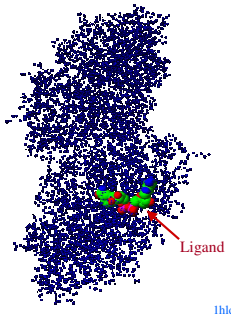

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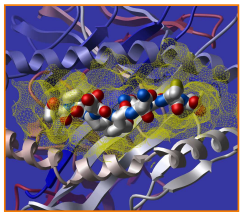
Protein-Ligand Docking

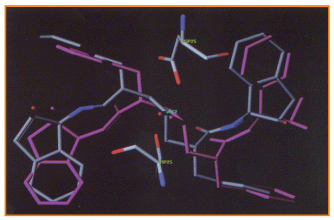
Goal:
- Given a protein and a ligand, determine the pose(s) and conformation(s) minimizing the total energy of the protein-ligand complex



http://www.molsoft.com/

Protein-Ligand Docking

Metric:
- How well do the predicted poses and conformations match measured ones (e.g., RMSD)



[Jones97]

Protein-Ligand Docking

Challenges:

- Predicting energetics of protein-ligand binding
- Searching space of possible poses & conformations

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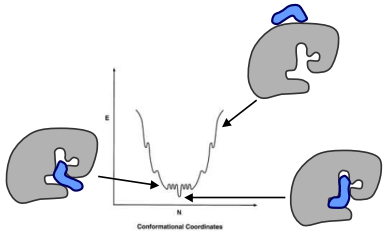
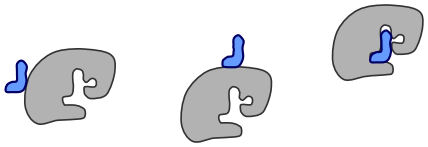


Protein-Ligand Docking

Challenges:

- Predicting energetics of protein-ligand binding
- Searching space of possible poses & conformations
  - Ø Relative position (3 degrees of freedom)



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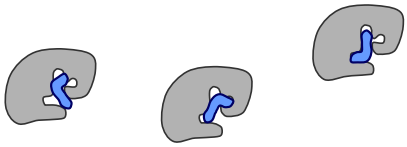

Protein-Ligand Docking

Challenges:

- Predicting energetics of protein-ligand binding
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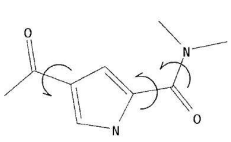

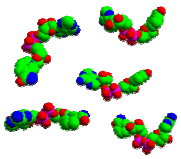

Protein-Ligand Docking

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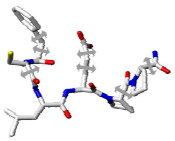
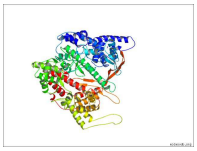
  - Ø Rotatable bonds in protein (m degrees of freedom)



Side chain movements



Large-scale movements

Outline

Introduction

Scoring functions
- Molecular mechanics
- Empirical functions
- Knowledge-based

Searching poses & conformations
- Systematic search
- Molecular dynamics
- Simulated annealing
- Genetic algorithms
- Incremental construction
- Rotamer libraries

Results & Discussion

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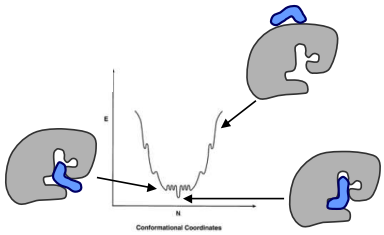
Results & Discussion

Scoring Functions

Goal: estimate binding affinity for given protein, ligand, pose, and conformations



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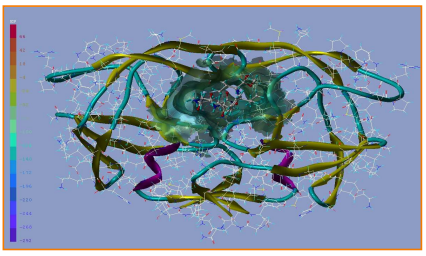
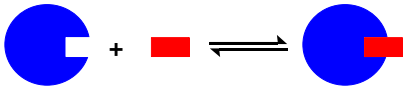


HIV-1 protease complexed with an hydroxyethylene isostere inhibitor [Marsden04]

Fundamental Forces of Binding



Binding Equations:

$R + L \underset{K_d}{\overset{K_a}{\rightleftharpoons}} R'L'$ $\qquad K_a = K_d^{-1} = \frac{[R'L']}{[R][L]}$

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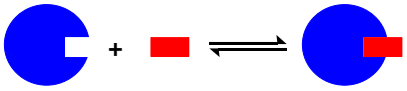

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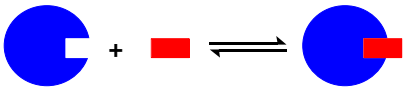

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enthalpy entropy

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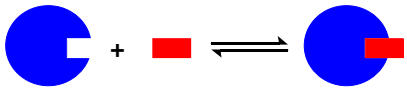

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K_a : 10^{-2} – 10^{-12} M
ΔG^o : -10 to -70 kcal/mol

enthalpy entropy

Factors Affecting ΔG^o

Intramolecular Forces (covalent)
- Bond lengths
- Bond angles
- Dihedral angles

Intermolecular Forces (noncovalent)
- Electrostatics
- Dipolar interactions
- Hydrogen bonding
- Hydrophobicity
- van der Waals

ΔH and ΔS work against each other in many situations.

Intramolecular Forces

Bond lengths (Å):

H – C 1.09	C – C 1.54	C – N 1.47
H – N 1.01	C = C 1.34	C – O 1.43
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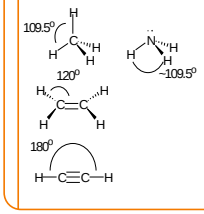

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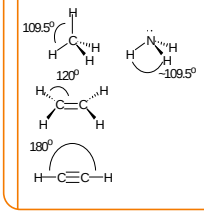
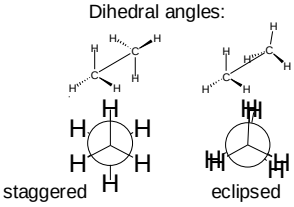


Dihedral angles:



staggered eclipsed

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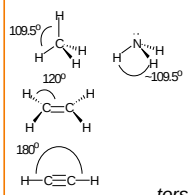

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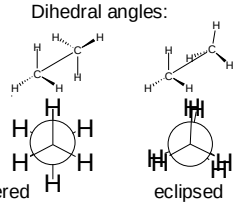
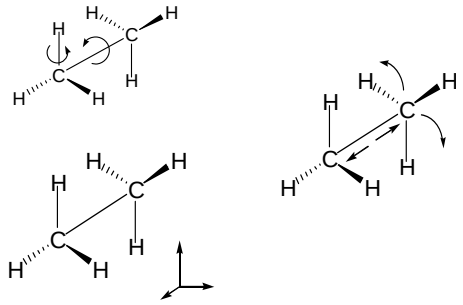


staggered eclipsed

torsional strain energy (eclipsed: 1 kcal/mol)

Entropic Effects of Ligand Binding



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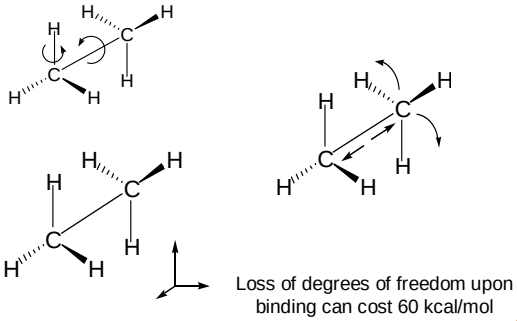


Loss of degrees of freedom upon binding can cost 60 kcal/mol

Intermolecular Forces

Electrostatic interactions

Dipolar interactions

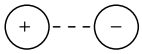
Hydrogen bonding

Hydrophobicity

van der Waals associations

Electrostatics

Charge-charge
- pH dependence



Charge-dipole

Charge-induced dipole

Electrostatics

Charge-charge
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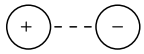

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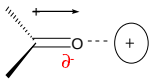

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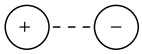

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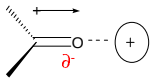

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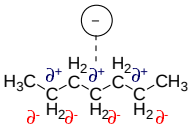
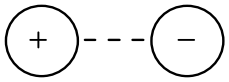
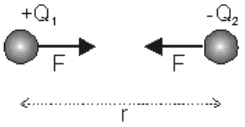
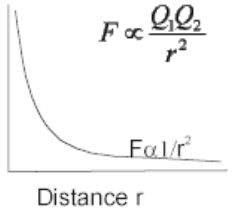


Coulomb's Law



charge-charge

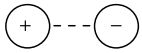




http://www.plus2physics.com/electrostatics/study_material.asp

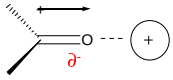
Electrostatics

Charge-charge
- pH dependence



4-7 kcal/mol

Charge-dipole



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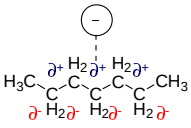
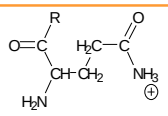
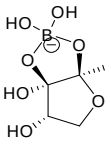


increasing distance dependence

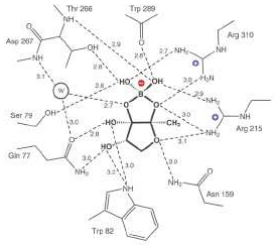
Coulombic Interactions in Ligand Binding



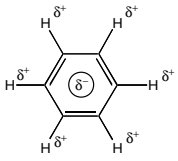
arginine

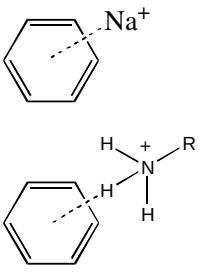


ligand



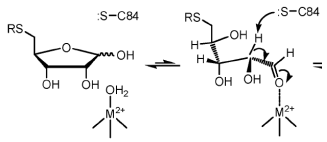
Cation-π Interactions



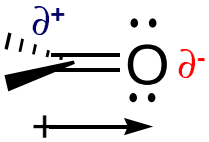


http://www.owlnet.rice.edu/~chem547/lectures/lecture04.ppt#257,5,Slide 5

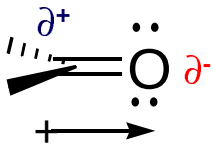
Interactions with Metal Ions

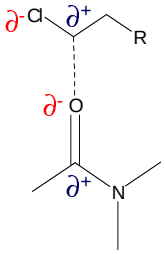


Dipolar Interactions



Dipole-Dipole Interactions





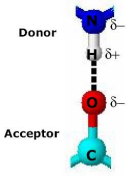
0.1 – 1 kcal/mol

Hydrogen Bonding

2.5-3.2 Å

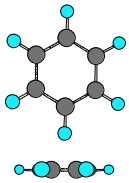
highly directional
(130° ≤ Θ ≤ 180°)

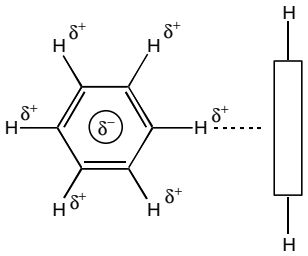
2-10 kcal stabilization



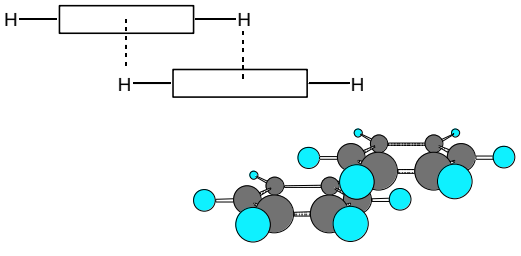
also O-H, F-H, even C-H

π-Stacking Interactions: End-to-Face

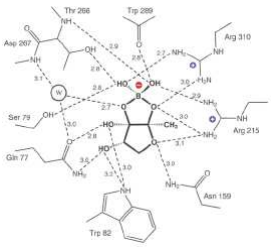




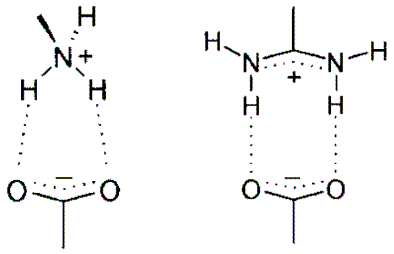
π-Stacking Interactions: Face to Face



Hydrogen Bonding in Ligand Binding



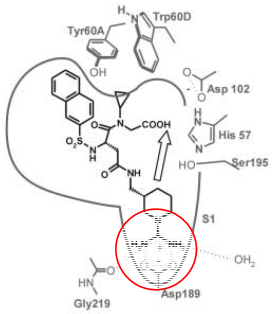
Salt Bridges



energetics similar to H-bonds (2-10 kcal/mol)

[Klebe02]

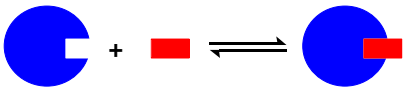
Salt Bridges in Ligand Binding



Binding of napsagatran to thrombin

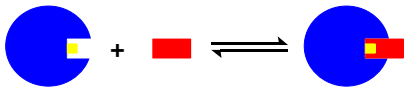
[Klebe02]

Hydrophobicity



Binding pocket becomes “interior” upon complexation with ligand

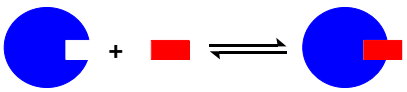
Hydrophobicity



Binding pocket becomes “interior” upon complexation with ligand

Big penalty: charged or polar groups buried but unpaired

Hydrophobicity



Binding pocket becomes “interior” upon complexation with ligand

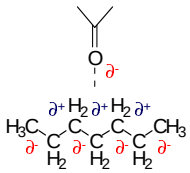
Big penalty: charged or polar groups buried but unpaired

Energetic contribution is propotional to the size of the surface buried upon ligand binding

- e.g. $-CH_3$ group (25 Å^2): 3 to 6 kcal/mol

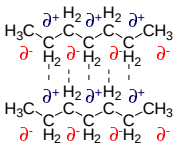
van der Waals Interactions

Dipole – induced dipole



Distance dependent

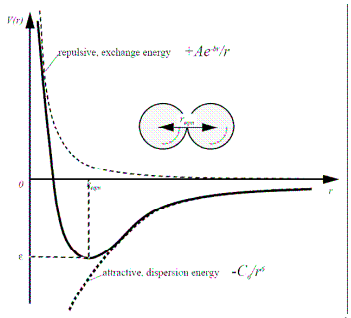
Induced dipole – induced dipole



Short-range repulsion

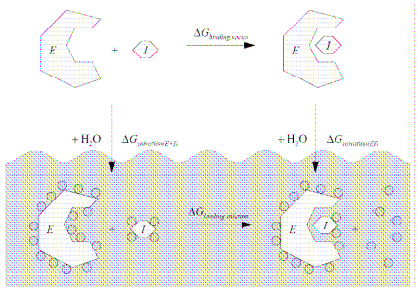
stabilization > 1 kcal/mol

van der Waals Interactions



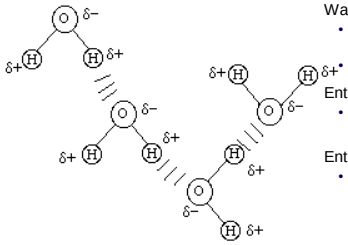
AutoDock User's Manual

Solvation and Desolvation



AutoDock User's Manual

Solvent Effects: Hydrogen Bonding



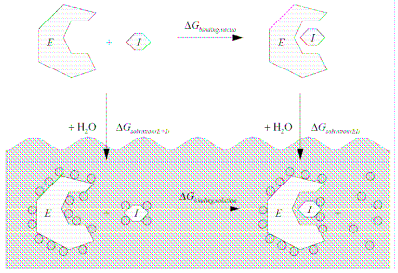
Water
- tetrahedrally connected network
- very small volume

Enthalpy:
- 3 – 4 H-bonds at 2 – 10 kcal/mol each

Entropy:
- flexible matrix (disorder)

http://www.bgsu.edu/departments/chem/midden/MITBCT/chem/review.html#Hbonds

Solvation and Desolvation

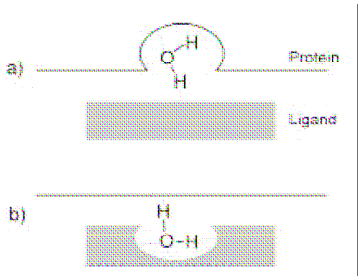


Rupture H-bonds within water matrix
Reorganize water molecules at surface
Lose degrees of freedom

Reform H-bonds
Bury a hydrophobic pocket surface
Some water molecules released

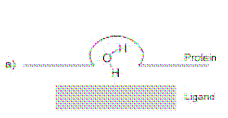
AutoDock User's Manual

Solvent Effects: Solvent-Assisted Binding

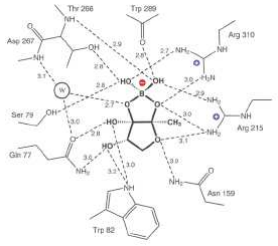


[Klebe02]

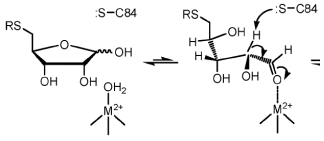
Solvent-Assisted Binding



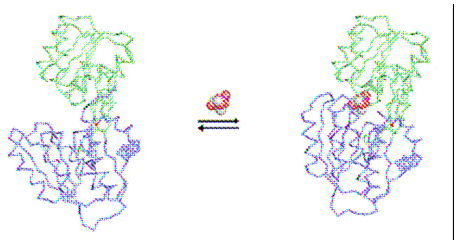
"interstitial waters"



Solvent Displacement



Protein Conformation



Fewer degrees of freedom
New interaction surfaces
Usually driven by hydrophobicity

Scoring Functions

Molecular mechanics force fields:
- CHARMM [Brooks83]
- AMBER [Cornell95]

Empirical methods:
- ChemScore [Eldridge97]
- GlideScore [Friesner04]
- AutoDock [Morris98]

Knowledge-based methods
- PMF [Muegge99]
- Bleep [Mitchell99]
- DrugScore [Gohlke00]

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Molecular Mechanics Force Fields

CHARMM:

$$U\left(\vec{R}\right) = \sum_{\text{bonds}} K_b\left(b-b_0\right)^2 + \sum_{\text{UB}} K_{UB}\left(S-S_0\right)^2 + \sum_{\text{angle}} K_\theta\left(\theta-\theta_0\right)^2 + \sum_{\text{dihedrals}} K_\chi\left(1+\cos\left(n\chi-\delta\right)\right) + \sum_{\text{impropers}} K_{\text{imp}}\left(\phi-\phi_0\right)^2 + \sum_{\text{nonbond}} \epsilon\left[\left(\frac{R_{min_{ij}}}{r}\right)^{12} - \left(\frac{R_{min_{ij}}}{r}\right)^{6}\right] + \frac{q_i q_j}{\epsilon_1 r_{ij}}$$

K_b, K_{UB}, K_θ, K_χ, K_{imp} are constants, b is the bond length, b_0 is the equilibrium bond length, S is the UB 1,3-distance, S_0 is the ideal UB 1,3-distnace, θ is the angle value, θ_0 is the equilibrium angle value, χ is the dihedral angle value, n is the periodicity, ϕ is the improper angle value, ϕ_0 is the ideal improper angle value, r is the Lennard-Jones well depth, $R_{min_{ij}}$ is the distance at the Lennard Jones minimum, q_i and q_j are the atoms' charge ϵ_1 is the effective dielectric constant, r_{ij} is the distance between the atoms

[Brooks83]

Molecular Mechanics Force Fields

AMBER:

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

K_r, K_θ, V_n, A_{ij}, B_{ij}, C_{ij}, D_{ij} are constants, r is the bond length, r_{eq} is the equilibrium bond length, θ is the angle value, θ_{eq} is the equilibrium angle value, ϕ is the dihedral angle value, n is the periodicity, q_i and q_j are the atoms' charge ϵ is the effective dielectric constant, R_{ij} is the distance between the atoms

[Cornell95]

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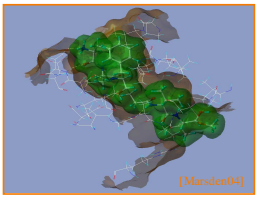
Empirical Scoring Functions

ChemScore:

$$\Delta G_{bind} = \Delta G_0 + \Delta G_{hbond} \sum_{iL} g_1(\Delta r) g_2(\Delta\alpha) + \Delta G_{metal} \sum_{aM} f(r_{aM}) + \Delta G_{lipo} \sum_{iL} f(r_{iL}) + \Delta G_{rot} H_{rot}$$



[Eldridge97]

Empirical Scoring Functions

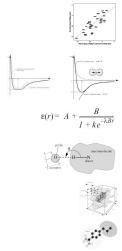
GlideScore:

$$\Delta G_{bind} = C_{hbond-neut-neut} \sum g(\Delta r) h(\Delta\alpha) + C_{hbond-neut-charged} \sum g(\Delta r) h(\Delta\alpha) + C_{hbond-charged-charged} \sum g(\Delta r) h(\Delta\alpha) + C_{max-metal-ion} \sum f(r_{lm}) h(\Delta\alpha) + C_{lipo-lipo} \sum f(r_{lr}) + C_{rotb} H_{rotb} + C_{polar-phob} V_{polar-phob} + C_{coul} E_{coul} + C_{vdW} E_{vdW} + solvation terms$$

[Friesner04]

Empirical Scoring Functions

AutoDock 3.0:



$$\Delta G_{binding} = \Delta G_{vdW} + \Delta G_{elec} + \Delta G_{hbond} + \Delta G_{desolv} + \Delta G_{tors}$$

ΔG_{vdW} 12-6 Lennard-Jones potential

ΔG_{elec} Coulombic with Solmajer-dielectric

ΔG_{hbond} 12-10 Potential with Goodford Directionality

ΔG_{desolv} Stouten Pairwise Atomic Solvation Parameters

ΔG_{tors} Number of rotatable bonds

[Huey & Morris, AutoDock & ADT Tutorial, 2005]

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Knowledge-Based Scoring Functions

DrugScore:

$$\Delta W = \gamma \left[\sum_{k_i} \sum_{l_j} \Delta W_{i,j}(r) \right] + (1-\gamma) \times \left[\sum_{k_i} \Delta W_i(SAS, SAS_0) + \sum_{l_j} \Delta W j(SAS, SAS_0) \right]$$

Protein-Ligand Atom Distance Term

Solvent Accessible Surface Terms

[Gohlke00]

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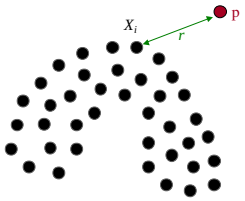
How to compute score efficiently?

Computing Scoring Functions

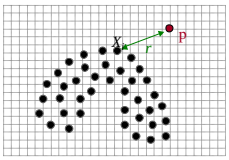
Point-based calculation:
- Sum terms computed at positions of ligand atoms (this will be slow)

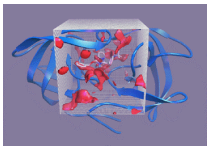


Computing Scoring Functions

Grid-based calculation:
- Precompute "force field" for each term of scoring function for each conformation of protein (usually only one)
- Sample force fields at positions of ligand atoms

ØAccelerate calculation of scoring function by 100X





[Huey & Morris]

Outline

Introduction

Scoring functions
- Molecular mechanics
- Empirical functions
- Knowledge-based

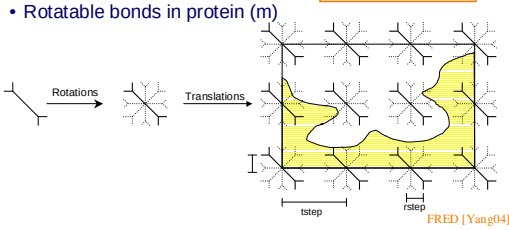
Searching poses & conformations ←
- Systematic search
- Molecular dynamics
- Simulated annealing
- Genetic algorithms
- Incremental construction
- Rotamer libraries

Results & Discussion

Systematic Search

Uniform sampling of search space
- Relative position (3)
- Relative orientation (3)
- Rotatable bonds in ligand (n)
- Rotatable bonds in protein (m)

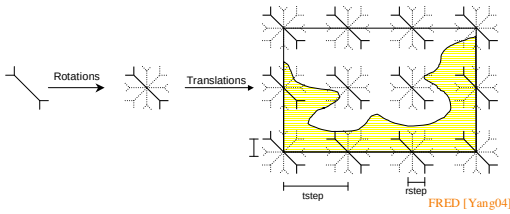
The search space has dimensionality $3 + 3 + r^n + r^m$



FRED [Yang04]

Systematic Search

Uniform sampling of search space
- Exhaustive, deterministic
- Quality dependent on granularity of sampling
- Feasible only for low-dimensional problems

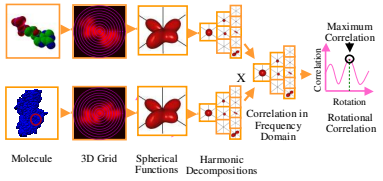


FRED [Yang04]

Systematic Search

Uniform sampling of search space

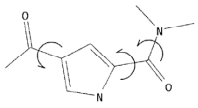
- Exhaustive, deterministic
- Quality dependent on granularity of sampling
- Feasible only for low-dimensional problems
  - § Example: search all rotations – Wigner-D^{-1}

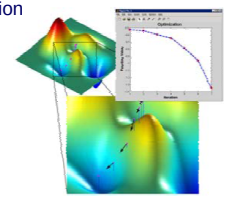


Molecular Mechanics

Energy minimization:

- Start from a random or specific state (position, orientation, conformation)
- Move in direction indicated by derivatives of energy function
- Stop when reach local minimum



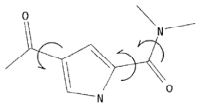


[Marai04]

Simulated Annealing

Monte Carlo search of parameter space:

- Start from a random or specific state (position, orientation, conformation)
- Make random state changes, accepting up-hill moves with probability dictated by "temperature"
- Reduce temperature after each move
- Stop after temperature gets very small

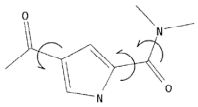


AutoDock 2.4 [Morris96]

Genetic Algorithm

Genetic search of parameter space:

- Start with a random population of states
- Perform random crossovers and mutations to make children
- Select children with highest scores to populate next generation
- Repeat for a number of iterations

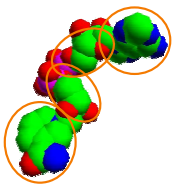


Gold [Jones95], AutoDock 3.0 [Morris98]

Incremental Extension

Greedy fragment-based construction:

- Partition ligand into fragments

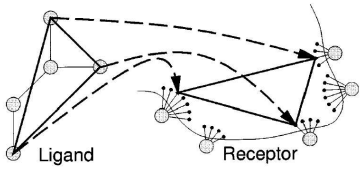


FlexX [Rarey96]

Incremental Extension

Greedy fragment-based construction:

- Partition ligand into fragments
- Place base fragment (e.g., with geometric hashing)

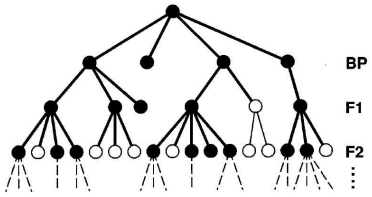


FlexX [Rarey96]

Incremental Extension

Greedy fragment-based construction:

- Partition ligand into fragments
- Place base fragment (e.g., with geometric hashing)
- Incrementally extend ligand by attaching fragments

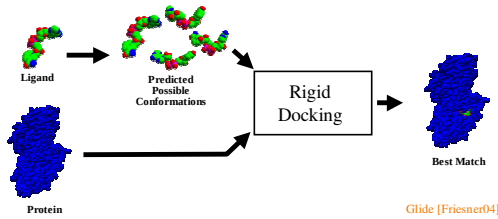


FlexX [Rarey96]

Rotamer Libraries

Rigid docking of
many conformations:

- Precompute all low-energy conformations
- Dock each precomputed conformations as rigid bodies

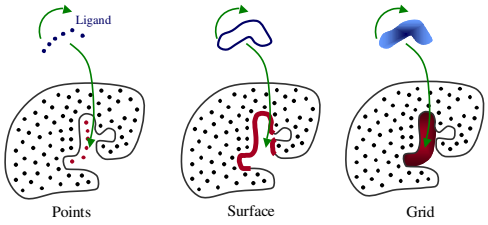


Glide [Friesner04]

Rigid Docking

This is just like matching binding sites (complement)

- Can use same methods we used for matching and indexing point, surface, and/or grid representations



Outline

Introduction

Scoring functions

- Molecular mechanics
- Empirical functions
- Knowledge-based

Searching poses & conformations

- Systematic search
- Molecular dynamics
- Simulated annealing
- Genetic algorithms
- Incremental construction
- Rotamer libraries

Results & Discussion

Discussion

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