

Molecular Mechanics & Dynamics

Introduction to Structural Bioinformatics

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Outline

- o Applications of Computed Structure
- o Molecular Mechanics
 - o Equations
 - o Minimization
 - o Limitations
- o Molecular Dynamics
 - o Algorithms
 - o Applications
 - o Free energy simulations
- o MD Examples:
 - o MD simulation of coiled coils
 - o Relative binding constants for HIV protease inhibitors

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Why Compute Structure?

- o HAVE: information about composition
WANT: two (connectivity) or three dimensional structure
- o HAVE: structure and physico-chemical properties
WANT: rationalization of their relationship
- o HAVE: information about the relationship
WANT: predict new structures/properties

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Central Postulate

Structure \equiv Energy

- o Any geometrical system has an associated Energy determined by its coordinates
- o A fundamental description includes a multidimensional potential energy surface
- o Minima on this surface correspond to stable configurations

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Computed Structure

- o General Problem: Locate the energy minima starting from arbitrarily chosen configuration
- o Need: mathematical description of structure/energy relationship
- o Structure: Cartesian or internal coordinates

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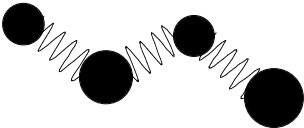
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Molecular Mechanics

- o Definition: A mathematical model to predict accurate structures and energies of molecules
- o Basic Concept: optimize the geometry of a molecule (computed bonds and bond angles) to adopt "natural" meanings and values

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MM View of Molecules



Molecules: masses joined by springs

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MM: Simple Chemical View

- o Molecules consist of atoms
- o Atoms are bonded to each other according to the rules of valence (bonded terms)
- o Molecules are flexible (torsional terms)
- o Non-bonded atoms interact with each other (non-bonded terms)

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MM Formula

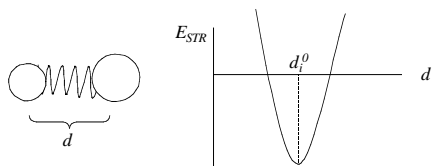
$$E = \sum E_{STR} + \sum E_{BEND} + \sum E_{OOP} + \sum E_{TOR} + \sum E_{VDW} + \sum E_{ELE}$$

STR = stretching; BEND = bending; OOP = out of plane bending
 TOR = torsional; VDW = van der Waals; ELE = electrostatic

The MM energy expression presents the relationship between Chemical structure and its energy.

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Bond Stretching Energy



$$E_{STR} = \sum_{i=1}^n \frac{1}{2} k^{d_i} (d_i - d_i^0)^2$$

d_i = length of i^{th} bond
 d_i^0 = equilibrium length of i^{th} bond
 k^{d_i} = bond stretching force constant

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Angle Bending Energy

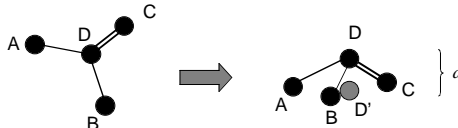


$$E_{BEND} = \sum_{i=1}^n \frac{1}{2} k^{\theta_i} (\theta_i - \theta_i^0)^2$$

θ_i = angle between two adjacent bonds
 θ_i^0 = equilibrium value for the i^{th} angle
 k^{θ_i} = angle bending force constant

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Out of Plane Bending Energy

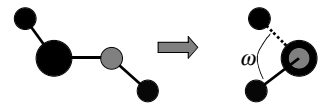


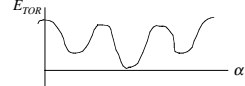
$$E_{OOP} = \sum_{i=1}^n \frac{1}{2} k_i^{OOP} d_i^2$$

d_i = distance between center atom and plane
 k^{OOP} = out of plane bending constant

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Torsional Energy

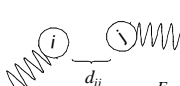


$$E_{TOR} = \frac{V_1}{2}(1 + \cos \omega) + \frac{V_2}{2}(1 - 2 \cos \omega) + \frac{V_3}{2}(1 + 3 \cos \omega)$$


V_1, V_2, V_3 = torsional barriers
 α = torsion angle

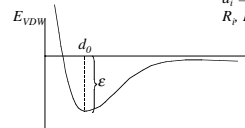
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van der Waals Energy



$$E_{VDW} = \sum_{i=1}^n \sum_{j=i+1}^n \epsilon \left[\left(\frac{d_{ij}}{R_i + R_j} \right)^{-12} - 2 \left(\frac{d_{ij}}{R_i + R_j} \right)^{-6} \right]$$

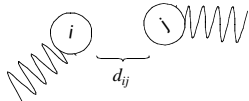
ϵ = van der Waals constant
 d_{ij} = distance between atoms i and j
 R_i, R_j = van der Waals radius of atoms i and j



$$E_{VDW} = \epsilon \left[\left(\frac{d_0}{d} \right)^{12} - 2 \left(\frac{d_0}{d} \right)^6 \right]$$

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Electrostatic Energy



$$E_{ELE} = \sum_{i=1}^n \sum_{j>i} \frac{Q_i Q_j}{4\pi\epsilon d_{ij}}$$

ϵ = dielectric constant
 d_{ij} = distance between atoms i and j
 Q_i, Q_j = net atomic charge at atoms i and j

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How to find a stable structure

- o Potential energy surface = multidimensional surface describing the energy of a molecule in terms of the nuclear positions
- o Algorithm:
 - o deform (twist, bend, stretch, pull...)
 - o calculate energy changes
 - o mathematically optimize (steepest descent, conjugate gradient...)
- o Result: nearest (local) energy minimum

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How to find a global minimum

- o Multi minimum problem: minimization only proceeds to lower energy and thus only finds minimum closest to starting point
- o Need to start from many independent (random) locations
- o Algorithms include Monte-Carlo simulations e.g.

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MM Optimization

$$E = \sum E_{STR} + \sum E_{BEND} + \sum E_{OOP} + \sum E_{TOR} + \sum E_{VDW} + \sum E_{ELE}$$

- o Structure and Energy are equivalent
- o Optimize Geometry & minimize Energy (don't mix them up!!)
- o Task: find stable conformers starting from arbitrary geometry
- o Molecular properties associated with ground state: heat of formation, vibrational spectra, shape (somewhat)

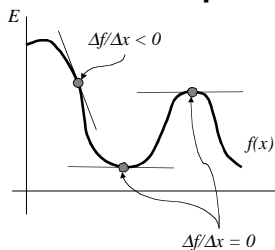
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MM Optimization [2]

- o Iterative geometry optimization always aims at lowering potential energy
- o Minimum energy depends on starting geometry
- o No known GENERAL method to find global minimum; only local minima closest to starting geometry are found

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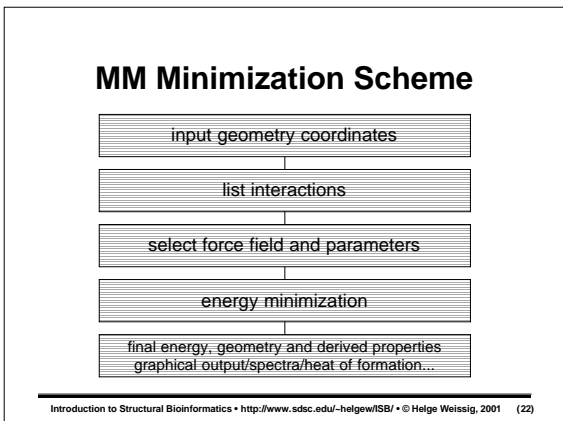
MM Optimization [3]



Numerically, finding energy minima involves identification of point(s) on the potential energy surface where the first derivatives are zero

This is true for local maxima as well!!!

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Cartesian/Internal Coordinates?

- o Need 3N coordinates for Cartesian v.
- 3N-6 for internal:

Internal:

1. Atom: center of coord. System
2. Atom: on one of the axes
-> one length
3. Atom: in the plane of that and 2nd axes
-> one length & one angle (α)
4. Atom: somewhere
-> one length, one angle (β) & one torsional angle (ω)

Cartesian coordinates are easier w/ forcefield terms!

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MM Notes

$$E = \sum E_{STR} + \sum E_{BEND} + \sum E_{DOOP} + \sum E_{TOR} + \sum E_{VDW} + \sum E_{ELE}$$

- o E is a steric energy, i.e. the difference between energies of ideal v. real molecule geometries
- o Numerical value of E is meaningless for comparisons between molecules
- o Equations and parameters are empirically derived. Parameters are adjustable and optimized for best fit between calculations and experiment.
- o Key assumption: parameters are transferable between molecules

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MM Limitations

- o MM will not:
 - o Provide parameters
 - o Calculate "natural" MM values (bonds, angles, charges ...)
 - o Handle unstable structures (e.g. transition states)
 - o Simulate structure modifications (chemical reactions)
 - o Account for conformation dependent charges
 - o Generally account for effects of re-distribution of electrons around nuclei.

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MM Cans & CANNOTs

<ul style="list-style-type: none">o Describe energy as a function of coordinates (i.e. enthalpy)o Allow atomic motion (minimization) but always downhill on the PE surfaceo Describe conformations and conformers	<ul style="list-style-type: none">o Describe energy as a function of time and temperature (i.e. entropy and free energy)o Allow atoms move uphill the PE surfaceo Describe conformational states (more realistic!)o Include important parameters of "molecular life": temperature, atomic mass, time
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Related to molecular motion!!

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Molecular Dynamics

- o Definition: computational technique that studies the motions of atoms and molecules that occur due to their interactions
- o Calculates fluctuations of atomic positions as a function of time
- o Obtains macroscopic properties of a system from microscopic interactions
- o "Snapshot": set of atomic coordinates at a certain moment during the simulation
- o "Trajectory": set of consecutive snapshots

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Motions in "real life"

- o Kinetic properties of liquids and solids (also cellular membranes!)
- o Reaction mechanisms
- o Solubilities
- o Thermodynamic properties
- o Binding
- o Folding of proteins, polymers, nucleic acids
- o MD: extension of classical MM modeling by application of Newtonian laws

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Protein Dynamics

t [s]

10⁻¹⁴ } Relative vibration of bonded atoms

10⁻¹² } Rotation of side chains at protein surface

10⁻⁹ } Torsional vibration of buried groups

10⁻⁶ } Relative motion of different globular regions

10⁻³ } Rotation of medium-sized side chains in protein interior

1 } Local denaturation

10

McCammeon & Harvey, 1987: Dynamics of Proteins and Nucleic Acids

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MD Success Applications

- Structure: position, distance & orientation
-> NMR & X-ray data refinement!!!!
- Mobility: B-factors, occupancy
- Dynamics: vibrational frequencies, relaxation rates, diffusion
- Thermodynamics: density, free energy, viscosity, conductance

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Basic Equations

- New position of atom i: $r_i(t + \Delta t) = r_i(t) + v_i \Delta t$
- Velocity of atom i: $v_i(t) = v_i(t - \Delta t) + a_i \Delta t$
- Acceleration of atom i: $a_i = \frac{F_i}{m_i}$
- Force at atom i: $F_i = \partial / \partial r_i E(r_1 \dots r_n)$
 $E(r_1 \dots r_n) =$ MM potential energy

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Temperature in MD

- Kinetic energy: $U_{kin} = \sum \frac{1}{2} m_i v_i^2 = \frac{3}{2} nkT$
 n = number of atoms
 k = Boltzmann constant
 T = absolute temperature
- Temperature is maintained by scaling of velocities at each MD step
- Typically 300K

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Temperature in MD [2]

- o Simulated annealing runs at higher T (e.g. 1000K) to enhance conformational sampling
- o Periodic cooling is used to settle into local minimum energy conformation
- o Most effective way for conformational sampling of large biopolymer systems

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MD Ensembles

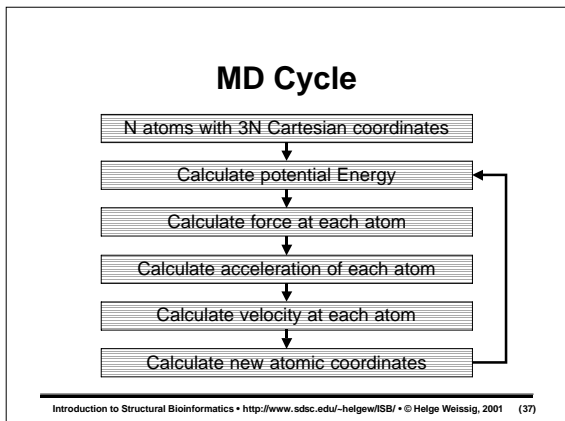
- o Constant Energy and volume (NVE)
- o Constant temperature and volume (NVT)
- o Constant temperature and pressure (NPT)

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MD Programs

- o AMBER: Weiner & Kollman, J. Comp. Chem. 2: 287 (1981)
- o CHARMM : Brooks et al., J. Comp. Chem. 4: 187 (1983)
- o GROMOS: van Gunsteren et al., PNAS 80: 4315 (1983)
- o DISCOVER: Hagler et al., J. Am. Chem. Soc. 96: 5319 (1974)
- o CEDAR: Carson & Hermans, in "Molecular Dynamics and Protein Structure", ed. J. Hermans (1985)

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MD Time Steps

- o Rule of thumb: use 1/10th of highest frequency motion (i.e. bond vibration, 10^{-14} s)
- o Resulting time steps:
$$\Delta t = 10^{-15} \text{ sec} = 1 \text{ fs} = 0.001 \text{ ps}$$
- o Fixed bond lengths (SHAKE method) allows increase to 2 fs

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Special Considerations

- o Long range interactions
 - o ~ n^2 non-bonded pairs
 - o List must be updated frequently (every 20-40 time steps)
 - o Truncate long range interaction with application of cutoff distance
 - o Alternatively: only allow atoms in active site to move, but still take immobile atoms' interactions into calculation!

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Special Considerations [2]

- o Solvent effects
 - o Continuum solvent model: assume $\epsilon = \epsilon_{i,j}$

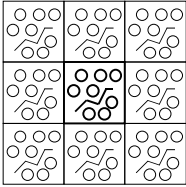
$$E_{ELE} = \sum_{i=1}^n \sum_{j>i}^n \frac{Q_i Q_j}{4\pi\epsilon d_{ij}} > E_{ELE} = \sum_{i=1}^n \sum_{j>i}^n \frac{Q_i Q_j}{4\pi d_{ij}^2}$$

- o Explicit solvent model: use specific, solvent dependent value for ϵ

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Special Considerations [3]

- o Solvent Effects (cont.)
 - o Periodic Boundary Conditions (PBC):
 - o Size of box is determined by dimensions of the solute molecule, D, and the cutoff distance R_{cutoff} : $S = D + 2R_{cutoff}$
 - o PBC allows for constant pressure if S is adjusted at each MD time step



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Typical MD Protocol

- o Describe the system
- o Describe MD features
- o Equilibrate the system
- o Run simulation
- o Analysis

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Typical MD Protocol [2]

- o Describe the system
 - o Define atomic positions
 - o Define system topology (connectivity)
 - o Define potential function (parameter file)
 - o Add missing atoms (H, hetero atoms...)
 - o Optimize geometry
 - o Add solvent, counter ions ...

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Typical MD Protocol [3]

- o Describe MD features
 - o Time step
 - o # of time steps (length of simulation)
 - o Frequency of non-bonded list update
 - o Conditions (T, V/P)
 - o Initial velocities
 - o Special considerations (PBC...)

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Typical MD Protocol [4]

- o Equilibrate the system
 - o Equilibrate solvent with solute
 - o Define # of heating and equilibration steps
 - o Monitor system properties (PE, KE, T, P) during heating and equilibration for convergence

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Typical MD Protocol [5]

- o Run simulation
 - o Specify save frequency for coordinates and velocities
 - o Monitor evolution of KE, PE, T, P
 - o Monitor desired parameters (RMSD, important distances...)

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Typical MD Protocol [6]

- o Analysis
 - o Structure stability
 - o Important molecular motions
 - o Average structure
 - o thermodynamics

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MD limitations

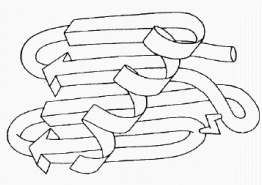
- o Very small time steps (1-2 fs)
- o Total simulation time 300 - 500 ps
- o Limited exploration of conformational space
- o Accumulation of numerical errors during simulation run

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MD limitations [2]

- o In general: MD modeling is good at predicting unrealistic structures

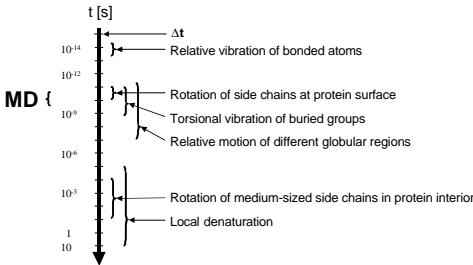
Incredulase



Richardson & Richardson: "Some design principles: Betabellin" in "Protein Engineering" (Oxender & Fox eds., 1987)

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MD in Protein Dynamics



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Alpha Helices

- o Each of the first four and last four residues forms only one intra-helical bond
- o Helices often begin and end with polar residues capable of making side chain/backbone H-bonds
- o Residues separated by two or three other residues are located on the same side of a α -helix (4-3 repeat)

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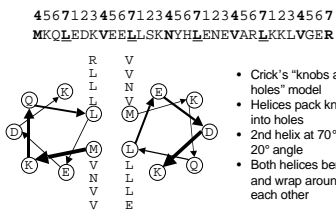
Coiled Coils

- o Coiled Coils: dimers of orientational parallel and in-register α -helices
- o Primary structure of coiled coils contain characteristic 4-3 hydrophobic repeats ($h^*h^*h^*h^*$)_n (n>4 in naturally occurring coiled coils)
- o Coiled coils are examples of simplest folded protein structure

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Coiled Coils [2]

- o Example: GCN4 peptide:



- Crick's "knobs and holes" model
- Helices pack knobs into holes
- 2nd helix at 70° or 20° angle
- Both helices bend and wrap around each other

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Coiled Coil Challenge

- o Design a dynamically stable, shorter coiled coil
- o Three-heptad, 22 residue coiled coil (P44)
- o Disulfide bridges stabilize N- and C-termini
- o MD simulations are run on crystallographic GCN4 structure and *de novo* designed structure
- o Role of disulfide bridges is analyzed by MD simulations after "cleavage" (deletion of connectivity records)

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Coiled Coil References

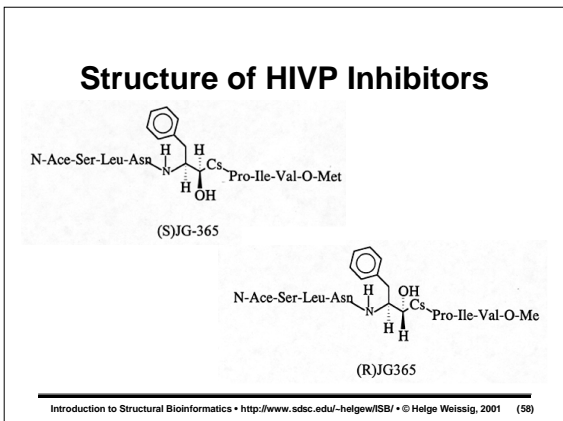
- o Theory:
 - o Crick, *Acta Cryst.* **6**: 685 (1953)
 - o Pauling & Corey, *Nature* **171**: 59 (1953)
- o Experiments:
 - o Zzta (O'Shea et al.)
- o Computer Simulations:
 - o Tropsha et al., *PNAS* **88**: 9488 (1991)
 - o Krystek et al., *Int. J. Peptide Protein Res.* **38**: 229 (1991)
 - o Nilges & Brunger, *Protein Eng.* **4**: 649 (1991)
 - o Treutlein et al., *Biochemistry* **31**: 12726 (1992)
 - o Rozzelle et al. *Protein Sci.* **3**: 345 (1994)

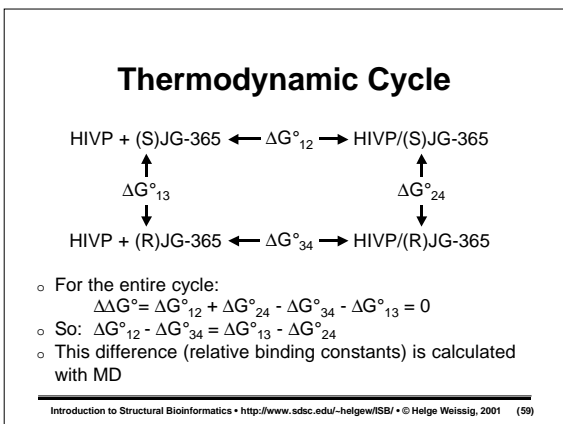
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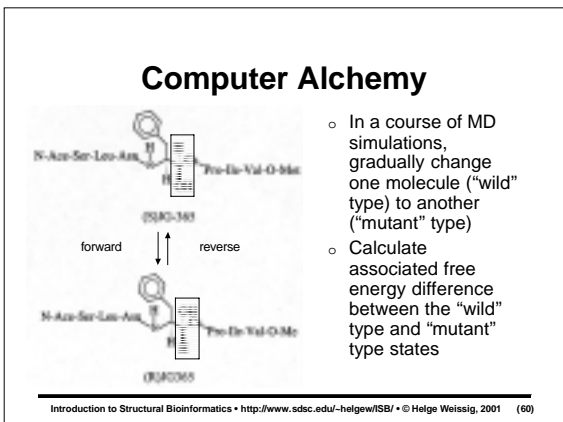
HIV Protease Inhibitors

- o Importance:
 - o Biological and pharmaceutical significance
 - o Abundance of structural information for both free enzyme and enzyme/inhibitor complexes
- o Task: calculation of relative binding constants

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Computer Alchemy [2]

- o To calculate free energy, the potential energy of the system is made dependent on an artificial parameter λ
- o λ is the relative contribution of one molecule and goes from 1 to 0 during the MD simulation:

$$E = E_{common} + \lambda E_{molecule\ 1} + (1 - \lambda) E_{molecule\ 2}$$

- o Thus:

$$\Delta G^{\circ}_{mol1,mol2} = \int_0^1 \frac{\partial E}{\partial \lambda} d\lambda \approx \sum_i \frac{\partial E}{\partial \lambda_i} \Delta \lambda$$

- o In practice $\Delta \lambda = 1/\Theta$ where Θ is the total simulation time

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MD Results

- | Theory | Experiment |
|--|--|
| o Tropsha & Hermans
(1992): -2.9 Kcal/mol | o Rich et al.
(1991): -2.6 Kcal/mol |
| o Ferguson et al.
(1991): -2.8 Kcal/mol | |

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