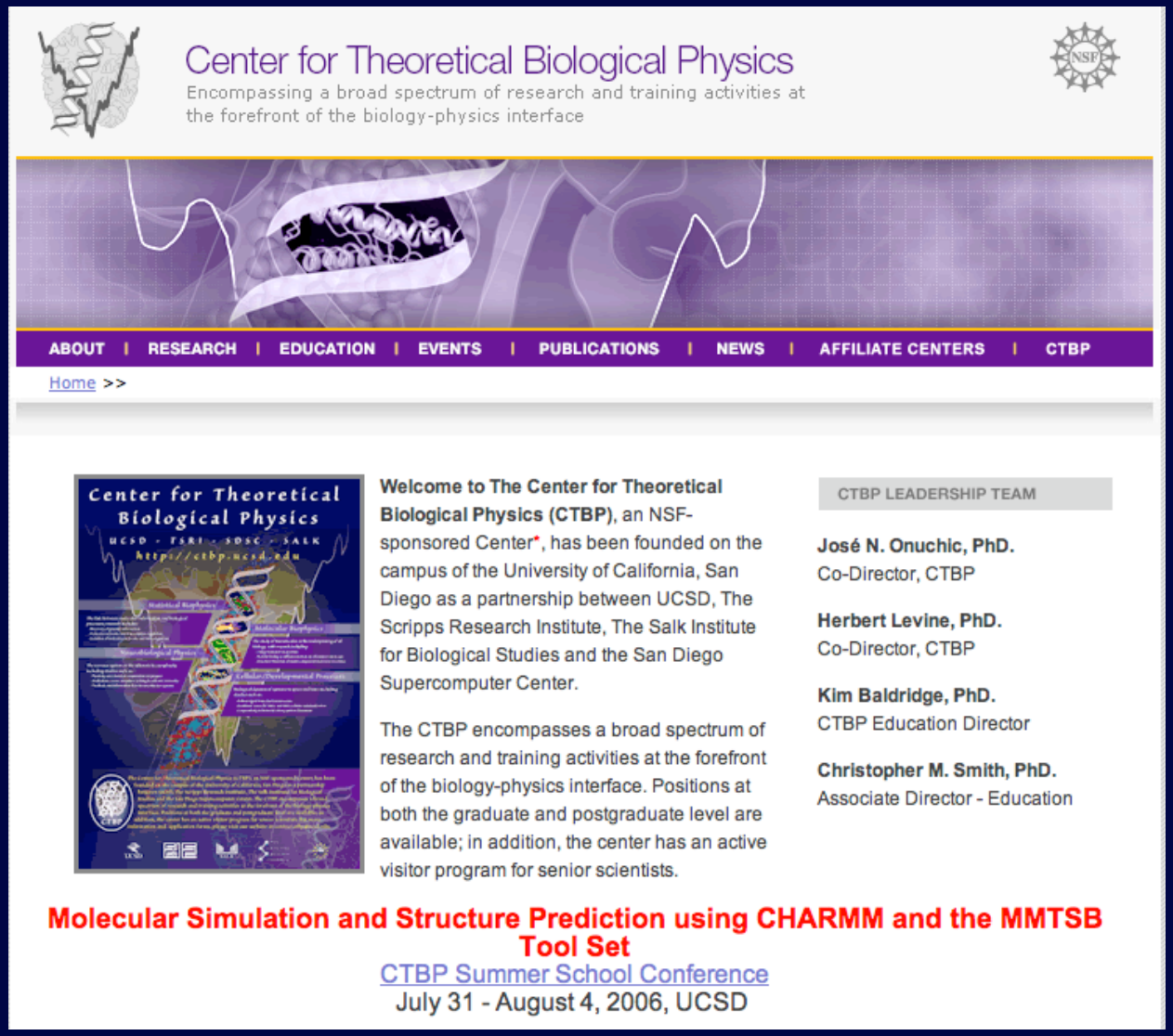
Molecular simulation and structure prediction using CHARMM, Amber and the MMTSB Tool Set
Introduction

Charles L. Brooks III
MMTSB/CTBP
2009 Summer Workshop

CTBP and MMTSB: Who are we?

- The CTBP is the Center for Theoretical Biological Physics
  - Funded by the NSF as a Physics Frontiers Center
  - Partnership between UCSD, University of Michigan and Salk, lead by UCSD
    - The CTBP encompasses a broad spectrum of research and training activities at the forefront of the biology-physics interface.
  - Principal scientists include
    - José Onuchic, Herbie Levine, Henry Abarbanel, Charles Brooks, Mike Holst, Terry Hwa, David Kleinfeld, Andy McCammon, Wouter Rappel, Terry Sejnowski, Wei Wang, Peter Wolynes

CTBP and MMTSB: Who are we?

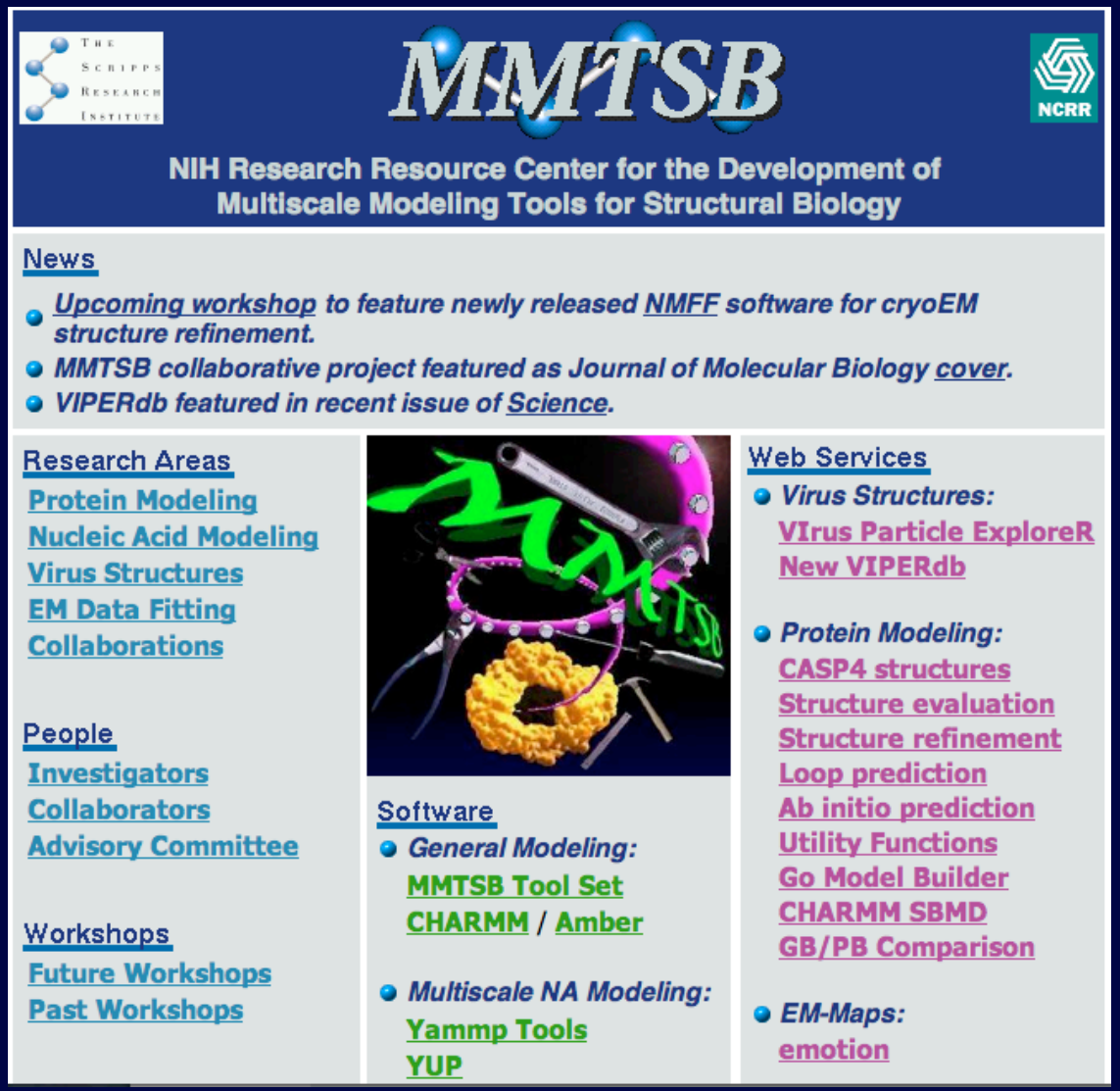


http://ctbp.ucsd.edu

CTBP and MMTSB: Who are we?

- The MMTSB is the Center for Multi-scale Modeling Tools for Structural Biology
  - Funded by the NIH as a National Research Resource Center
  - Partnership between University of Michigan, Rutgers University, Scripps and Georgia Tech, lead by University of Michigan
    - The MMTSB aims to develop new tools and theoretical models to aid molecular and structural biologists in interpreting their biological data.
  - Principal scientists include
    - Charles Brooks, David Case, Jack Johnson, Vijay Reddy, Jeff Skolnick

CTBP and MMTSB: Who are we?

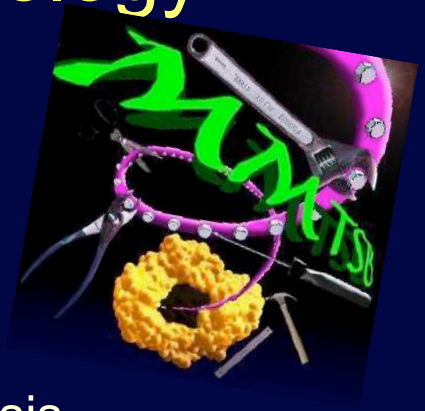


http://www.mmtsb.org

CTBP and MMTSB: Who are we?

- Activities
  - Fundamental research across a broad spectrum
  - Software and methods development and distribution
    - MMTSB distributes multiple software packages as well as hosts a variety of web services and databases
  - Training and research workshops and educational outreach
    - Both centers have extensive workshop programs
  - Visitors
    - Both centers host visitors and collaborators for short and longer term (sabbatical) visits

Center for the Development of Multi-scale Modeling Tools in Structural Biology (MMTSB)

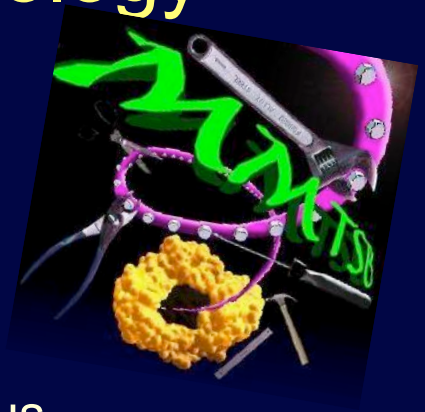


Overview of MMTSB activities

- Research
  - Virus assembly, maturation and structural analysis
  - Structure prediction and protein folding*
  - Homology modeling*
  - Protein, RNA and DNA modeling
  - Large-scale motions in biology
    - Functional displacements in the ribosome
    - Molecular motions from cryo-EM maps
    - Fitting atomic structures into EM densities

http://www.mmtsb.org

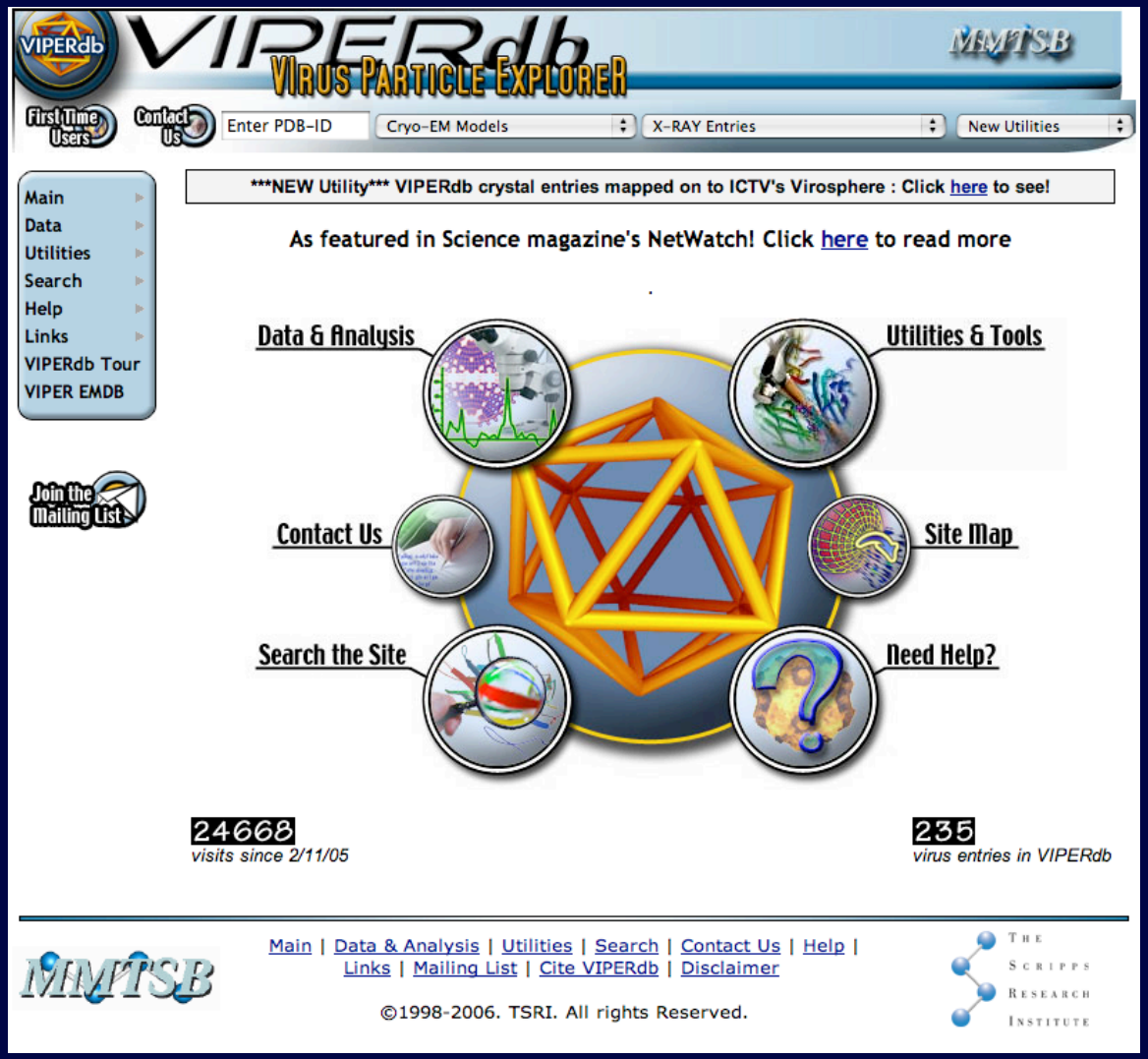
Center for the Development of Multi-scale Modeling Tools in Structural Biology (MMTSB)

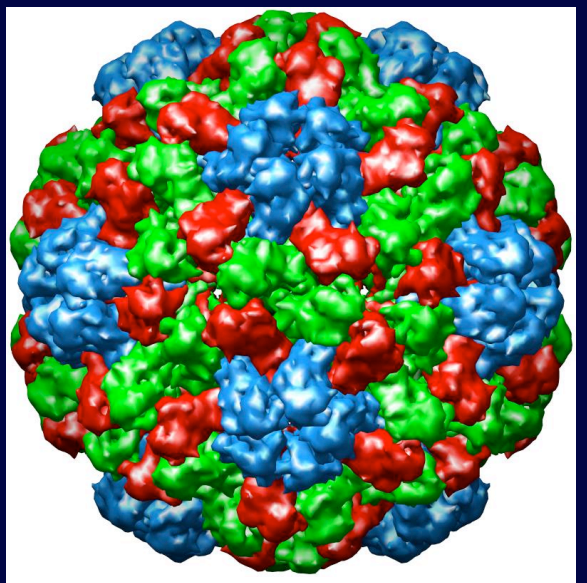


- Tools and resources
  - Virus Particle Explorer (ViPER) web-base of virus structures and assemblies
    - http://viperdb.scripps.edu
  - MMTSB computational structural biology toolset*
  - CHARMM, Amber, Situs, nab and YAMMP resource pages
  - NMFF - software package for flexibly fitting atomic structures into electron density maps from cryo-EM and tomography

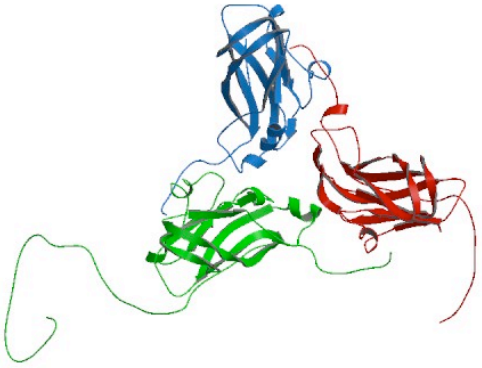
http://www.mmtsb.org

Virus Particle Explorer (VIPERdb)





Brome Mosaic Virus



http://viperdb.scripps.edu

Your instructors and mentors: Who are we?

- Charles Brooks
- David Case
- Michael Feig
- Jianhan Chen
- Jana K. Shen
- Ross Walker
  - All biophysicists involved in MMTSB and CHARMM/AMBER or MMTSB development
  - Jennifer Knight, Sishi Tang
    - Biophysicists working in Brooks/Case groups as postdoctoral collaborators

What is CHARMM?

- CHARMM is a software package for molecular simulation and analysis of proteins, nucleic acids, lipids, carbohydrates
  - Originated in the group of Martin Karplus at Harvard University circa 1975
  - Currently distributed in more than 1000 laboratories
  - Under continual development by more than 50 developers worldwide
  - CHARMM website and forum provide a venue to explore documentation, discuss results and get advice from advanced CHARMM users and developers
  - Original publication: J. Comp. Chem., 4, 187 (1983)
  - Revised paper: J. Comp. Chem., 30, 15xx (2009)

http://www.charmm.org

What is Amber?

- Amber is a suite of programs for molecular simulation and analysis of proteins, nucleic acids, lipids, carbohydrates
  - Originated in the group of Peter Kollman at UCSF circa 1980
  - Currently distributed in 100's of laboratories
  - Under continual development by more than 10 developers worldwide
  - Amber website and reflector provide a venue to explore documentation, discuss results and get advice from advanced Amber users and developers
  - Reference publication: J. Comp. Chem., 26, 1668(2005)

http://www.amber.org

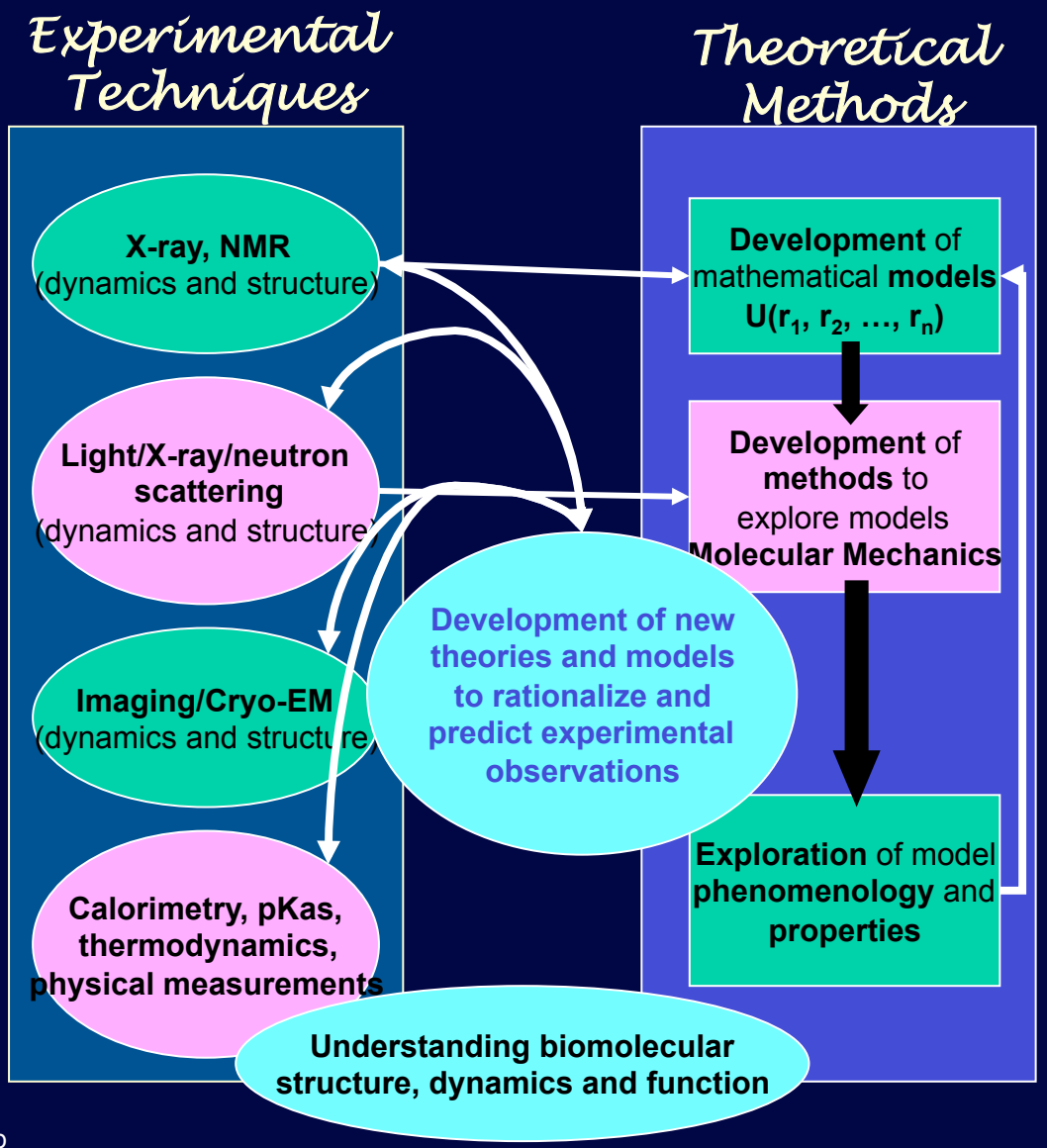
What is the MMTSB Tool Set?

- The MMTSB Tool Set is a collection of Perl-based scripts and modules that provide natural user interfaces to CHARMM, Amber, TASSSER, MODELLER, NAMD and other molecular modeling packages
  - Developed by M. Feig and J. Karanicolas in the Brooks group in 2002.
  - Currently downloaded more than 8000 times
  - Under development by in a number of laboratories
  - User forum as part of CHARMM forums
  - Original publication: J. Mol. Graph. Model., 22, 377 (2004)

http://www.mmtsb.org

Molecular Mechanics and Modeling

Molecular Mechanics and Modeling - Why



Overview and Objectives

- What is the basis of molecular mechanics?
  - Mathematical foundations: potential energy functions, energy minimization, molecular dynamics, implicit solvent, boundary conditions
- What are some uses of molecular simulations & modeling?
  - Conformational searching with MD and minimization
  - Exploration of biopolymer fluctuations and dynamics
  - MD as an ensemble sampler
- Free energy simulations
  - Energy minimization as an estimator of binding free energies
  - Application of FEP to protein stability
  - Approximate association free energy of molecular assemblies
  - Approximate pK_a calculations using continuum models

Basic elements of molecular modeling and molecular models

Mathematical Models - Force Fields

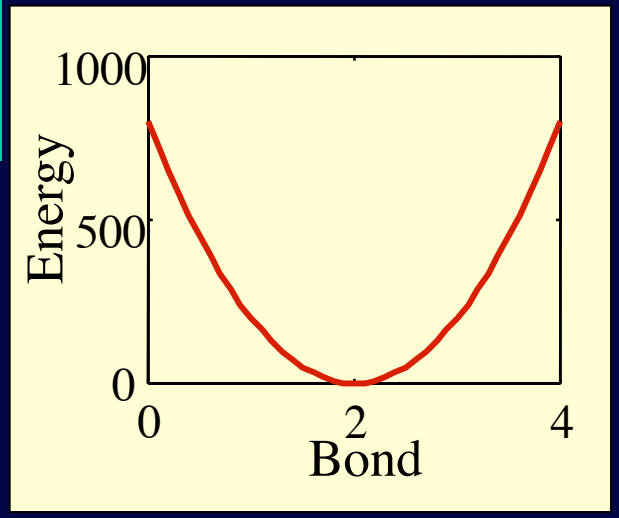
- MM force field is a compromise between speed and accuracy
- Force field is mathematical basis for expressing structure-energy relationships in biopolymers
- Common form (CHARMM, Amber, etc.):

$$U(\vec{r}_1,\vec{r}_2,\vec{r}_3,....,\vec{r}_N) = \sum_{\text{bonds, i}} \tfrac{1}{2} k_i^b \cdot (r_i - r_i^0)^2 + \sum_{\text{angles, i}} \tfrac{1}{2} k_i^\theta \cdot (\theta_i - \theta_i^0)^2$$

$$+ \sum_{\text{torsions, i}} k_i^\phi \cdot [1 + \cos(n_i \phi_i - \delta_i)]$$

$$+ \tfrac{1}{2} \sum_{\text{nonbondpairs, (i, j)}} \sum \left\{ \varepsilon_{\text{min}}^{\text{ij}} \left[\left(\frac{r_{\text{min}}^{ij}}{r_{ij}} \right)^{12} - 2 \left(\frac{r_{\text{min}}^{ij}}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{\varepsilon r_{ij}} \right\}$$

$$u_{bond} = \tfrac{1}{2} k_i^b \cdot (r_i - r_i^0)^2$$



- Energy terms - bonds

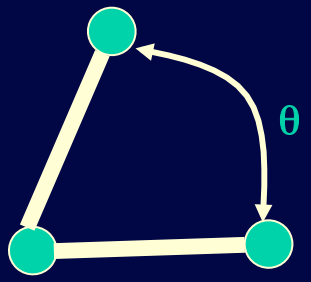
From spectroscopy, IR, etc.

Mathematical Models - Force Fields

- Angles

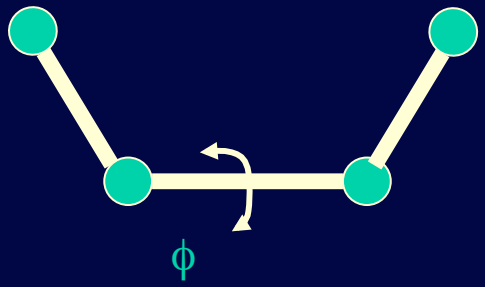
From spectroscopy, IR, etc.

$$u_{angle} = \tfrac{1}{2} k_i^{\theta} \cdot (\theta_i - \theta_i^0)^2$$

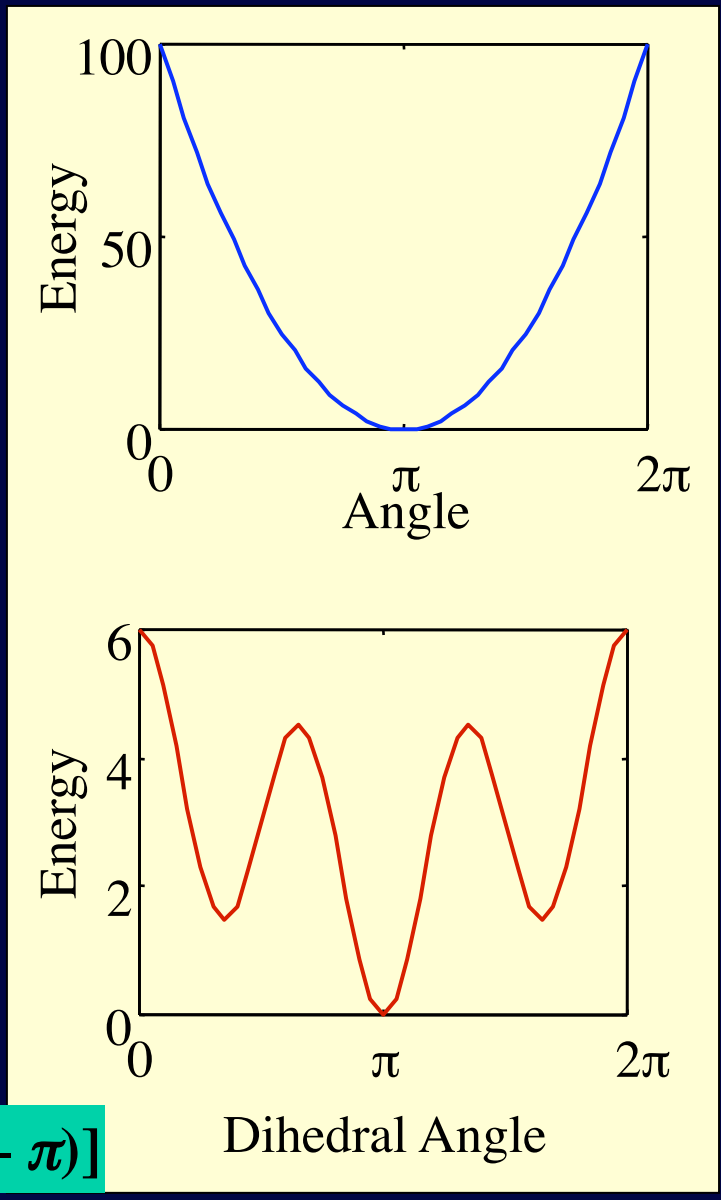


- Dihedrals

From spectroscopy, IR, NMR, empirical, QM



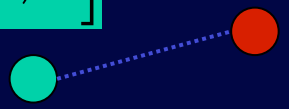
$$u_{dihedral} = k_i^{\phi} \cdot [1 + \cos(3\phi_i)] + k_i^{\phi'} \cdot [1 - \cos(\phi_i - \pi)]$$

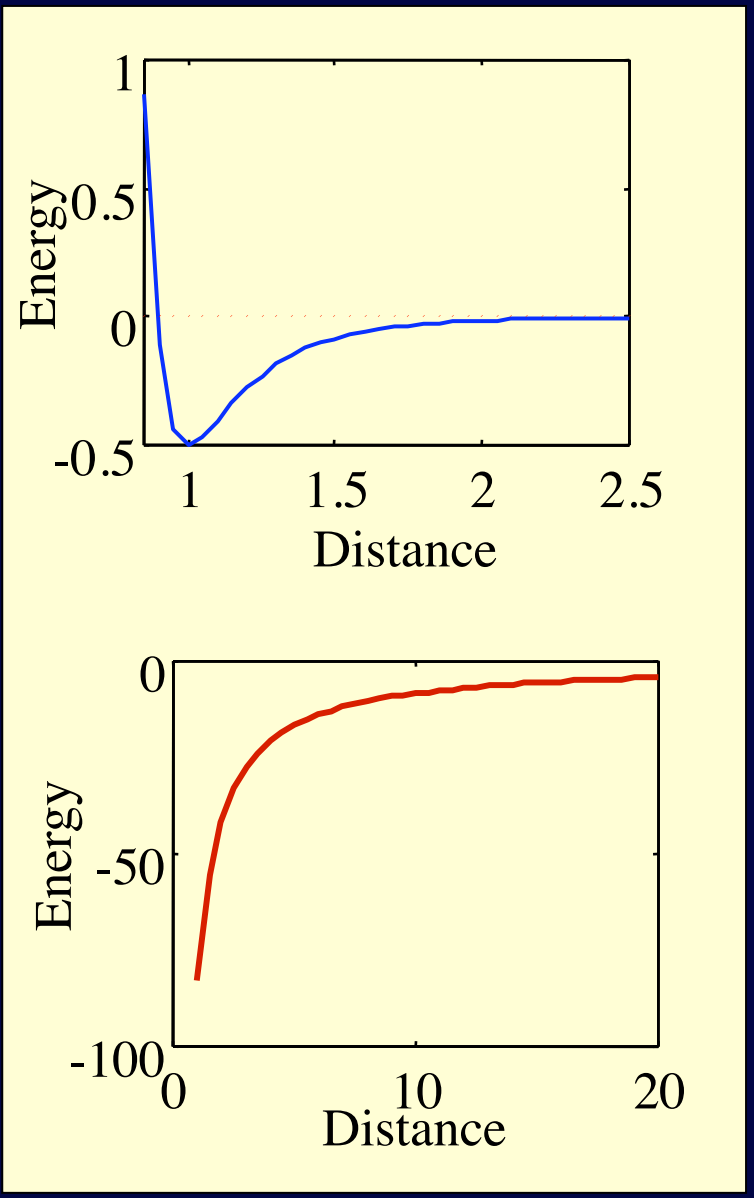


Mathematical Models - Force Fields

- Nonbonded - Lennard-Jones

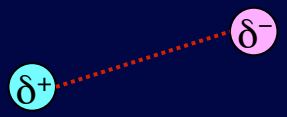
$$u_{L-J} = \varepsilon_{\min}^{ij}\left[\left(\frac{r_{\min}^{ij}}{r_{ij}}\right)^{12} - 2\left(\frac{r_{\min}^{ij}}{r_{ij}}\right)^{6}\right]$$





- Nonbonded - electrostatics

$$u_{Coulomb} = \frac{q_i q_j}{\varepsilon r_{ij}}$$



Non-bonded interactions derived from quantum chemistry, thermodynamics, empirical schemes

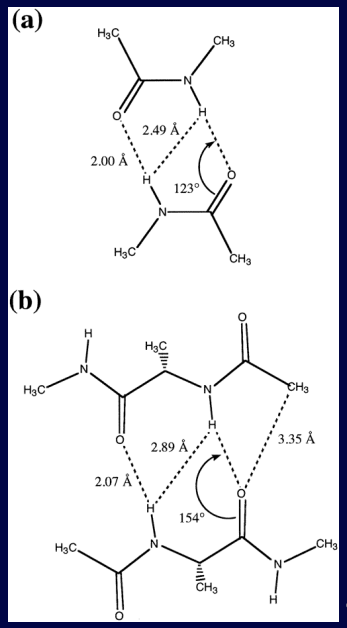
Assessing and deriving energy functions

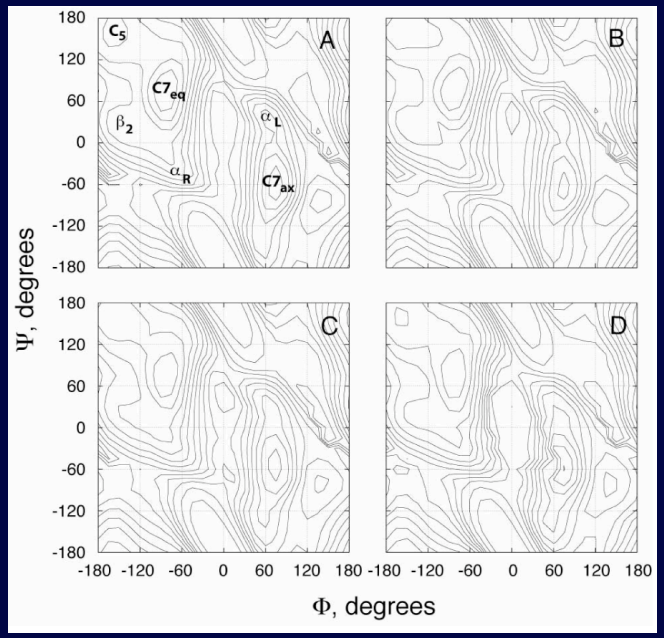
- Quantum chemistry provides means of deriving non-bonded energy functions
  - ϕ/ψ map for alanine dipeptide from QC calculations

Table 8. Interaction Energies (kcal/mol) of Two , β-Sheet Conformation Alanine Dipeptides[a]

MM3*(ε=1.5)	- 7.23
HF/cc-pVTZ(- f) (CP corrected)	- 8.15
MMFF(ε=2.0*r*)	- 8.24
HF/6-31G** (CP corrected)	- 9.25
HF/cc-pVTZ(- f) (non-CP corrected)	- 9.42
MM2*(ε=1.5)	- 9.69
MM3*	- 9.78
AMBER 3	- 9.84
MM3*(ε=1.0*r*)	- 10.23
LMP2/cc-pVTZ(- f) (HF CP corrected)	- 10.73
CVFF	- 10.77
MMFF(ε=1.5*r*)	- 11.01
AMBER*	- 11.07
HF/6-31G** (non-CP corrected)	- 11.68
LMP2/cc-pVTZ(- f) (HF non-CP corrected)	- 12.00
CFF95	- 12.14
AMBER*(ε=1.0*r*)	- 12.98
MSI CHARMm	- 12.99
MM2*	- 13.02
OPLS-AA(2,2)	- 13.21
MM2*(ε=1.0*r*)	- 13.47
CHARMM 22	- 14.10
MMFFs	- 14.97
CHARMM 19	- 15.21
MMFF	- 15.38
AMBER94	- 16.01
MM2X	- 16.11
AMBER94(ε=1.0*r*)	- 16.50
OPLS/A-UA(2,8)	- 16.70
OPLS-UA(2,2)	- 16.91
OPLS*	- 17.63

[a] Unless otherwise specified, ε= 1.0.





- Quantum chemistry provides "tests" of force fields

M.D. Beachey et al., *JACS*, **119**, 5908 ('97)
M. Feig et al., *JPCB*, **107**, 2831 ('03)
A. MacKerell et al., JCC, 25,1400 ('04)

Adding Charge Polarization via Charge Equalization

•*Electrostatic Potential Energy*

Patel & Brooks, *JCC*, **24**, 1, 2004

$$E_{electrostatic} = \sum_{i=1}^{N} \chi_i^0 Q_i + \frac{1}{2} \sum_{i=1}^{N} \sum_{j=1}^{N} \eta_{ij} Q_i Q_j$$

equilibrium charge density

penalty for perturbation from equilibrium due to presence of field

Distance dependent coulomb shielding

1-2 (Bond Atoms)
1-3 (Angle Atoms)
1-4 (Dihedral Atoms)

$$\eta(R_{ij}) = \frac{\frac{1}{2}(\eta_i + \eta_j)}{\sqrt{1.0 + \frac{1}{4}(R_i + R_j)^2}}$$

•*Parameterization of η and χ^o*

$$\eta \Delta\overline{Q} = -\overline{\phi} \quad \Rightarrow$$

$$\Delta\overline{Q} = -\eta^{-1}\overline{\phi}$$

ΔQ is the difference of the partial charge of an atom due to an applied external potential, φ_k, relative to vacuum

Decouples fitting of η and χ

•*Objective Function*

$$\varepsilon = \left\| \left(\Delta Q^{DFT} - \Delta Q^{FQ} \right) \right\|$$

Hardness parameters scaled to reduce condensed phase polarizability—represents confinement of diffuse tails of molecular electronic density due to Pauli repulsion in dense liquid (perhaps a universal need to employ reduced polarizabilities in classical simulations incorporating polarization).

Electronic Polarization: Fluctuating Charge Dynamics

- *Extended Lagrangian Formulation*

$$L = \sum_{i=1}^{M}\sum_{\alpha=1}^{N_i}\frac{1}{2}m_{i\alpha}\dot{r}_{i\alpha}^2 + \sum_{i=1}^{M}\sum_{\alpha=1}^{N_i}\frac{1}{2}m_{Q,i\alpha}\dot{Q}_{i\alpha}^2 - E(Q,r) - \sum_{i=1}^{M}\lambda_i\sum_{\alpha=1}^{N_i}Q_{i\alpha}$$

- *Charge Equations of Motion*

$$m_{Q,i\alpha}\ddot{Q}_{i\alpha} = -\frac{\partial E(\bar{Q},\bar{r})}{\partial Q_{i\alpha}} - \lambda_i$$

Total charge on molecule 'i' constant

$$\sum_{i=1}^{M}\sum_{\alpha=1}^{N_i}\ddot{Q}_{i\alpha} = 0$$

$$\lambda_i = -\frac{\sum_{\alpha=1}^{N_i}\frac{\partial E(\bar{Q},\bar{r})}{\partial Q_{i\alpha}}}{N_i} = -\frac{\sum_{\alpha=1}^{N_i}(\tilde{\chi}_{i\alpha})}{N_i}$$

average electronegativity of molecule 'i'

- *Charge Evolution/Dynamics*

$$m_{Q,i\alpha}\ddot{Q}_{i\alpha} = -\frac{\sum_{\beta=1}^{N_i}(\tilde{\chi}_{i\alpha} - \tilde{\chi}_{i\beta})}{N_i}$$

force on charge 'a' is proportional to the difference between the instantaneous site and average molecular electronegativities

Parameterization of Non-Electrostatic Parameters (Protein Force Field)

$$U = U_{bonds} + U_{angles} + U_{dihedrals} + U_{cross}$$
$$+ \sum_{\substack{non-bonded \\ atom\ pairs}} (U_{dispersion} + \frac{q_i q_j}{\varepsilon r_{ij}})$$

Scaling of polarizability

Electrostatic Parameters

Vacuum Water-Solute Dimers:
Geometries, Energies

CHARMM atom types

Bulk Liquid Properties:
(vaporization enthalpy, density)

- solute-solvent and solute-solute energetics
- solvent=TIP4P-FQ (protein ff intimately coupled to solvent model)

van der Waals (dispersion)

Backbone Torsion, Angle,Bond,
intra-molecular dispersion interactions

Protein Molecular Dynamics
(drift from native structure)

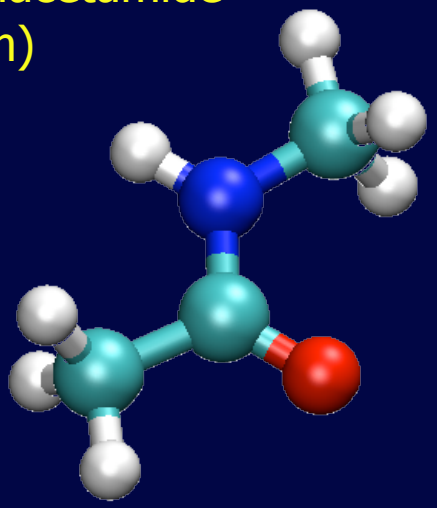
Patel et al., *JCC*, **24**, 1504, 2004

Electronic Polarization - deriving parameters

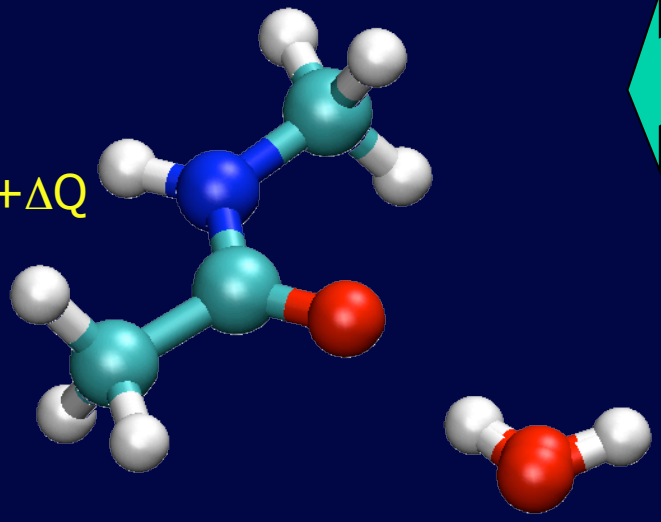
Charge Equilibration/Electronegativity Equalization

N-Methylacetamide
(vacuum)

Q^o



$Q=Q^o+\Delta Q$



- Equilibrium distribution of charges (i.e. vacuum)
- Redistribution of charge gives rise to electronic polarization (charge flow maintains electronegativity equalization)
- Directionality of charge flow - atomic electronegativity
- ΔQ governed by measure of resistance to charge flow to/from a given site-atomic hardness
- Polarizability <---> ΔQ

Molecular Mechanics
The Basic Algorithms

Demystifying Molecular Mechanics - Energy Minimization

- Minimization follows gradient of potential to identify stable points on energy surface
  - Let $\mathbf{U(x) = a/2(x-x_0)^2}$
  - Begin at **x'**, how do we find $\mathbf{x_0}$ if we don't know **U(x)** in detail?
    - How can we move from **x'** to $\mathbf{x_0}$?
  - Steepest descent based algorithms (SD):
    - $\mathbf{x \rightarrow x' = x+\delta}$
    - $\mathbf{\delta = -\kappa \partial U(x)/ \partial x = -\kappa a(x- x_0)}$
  - This moves us, depending on κ, toward the minimum.
  - On a simple harmonic surface, we will reach the minimum, $\mathbf{x_0}$, i.e. converge, in a certain number of steps related to κ.
- SD methods use first derivatives only
- SD methods are useful for large systems with large forces

Demystifying Molecular Mechanics - Energy Minimization

- Related Conjugate gradient methods
  - For this algorithm:
    - $x_n \rightarrow x_{n+1} = x_n + \alpha\delta_n$; $\delta_n = -\nabla_n U(x) + \delta_{n-1} A$
    - $$A = \frac{|\nabla_n U|^2}{|\nabla_{n-1} U|^2}$$
  - A related method is the Fletcher-Powell minimizer
- CG and Powell methods use first derivatives only
- Newton-Raphson (NR) and adopted basis NR (ABNR) use 2nd derivatives

$$\text{NR algorithm}: \; x_{n+1} = x_n + \delta_n$$
$$\delta_n = -(\nabla_n U)/(\nabla_n \nabla_n U)$$

  - For our 1-D example:
  - $\delta_n = -a(x_n - x_0)/a = x_0 - x_n$
- ABNR approximates 2nd derivatives
- Best near minimum

Demystifying Molecular Mechanics - Molecular Dynamics

- Molecular dynamics
- Objective: $(r_1(t), \ldots, r_N(t)) \rightarrow (r_1(t+\Delta t), \ldots, r_N(t+\Delta t))$
- The Verlet central difference scheme (L Verlet, J. Chem. Phys., 1967

• expand $x(t \pm \Delta t)$ in Taylor's series around t

$$x(t \pm \Delta t) = x(t) \pm v(t)\Delta t + \frac{1}{2m} f(t)\Delta t^2 \pm \frac{1}{6}\dddot{x}(t)\Delta t^3 + O(\Delta t^4)$$

• add expansion $x(t + \Delta t)$ and $x(t - \Delta t)$ and rearrange

$$x(t + \Delta t) = 2x(t) - x(t - \Delta t) + \frac{f(t)}{m}\Delta t^2 + O(\Delta t^4) \text{ (position propagation)}$$

• add expansion $x(t - \Delta t)$ and $x(t + \Delta t)$ and rearrange

$$v(t) = (x(t + \Delta t) - x(t - \Delta t)/(2\Delta t) + O(\Delta t^3) \text{ (velocity propagation)}$$

Demystifying Molecular Mechanics - Molecular Dynamics

- Other "summed forms"
  - Leap-frog

$$x(t+\Delta t) = x(t) + \Delta t \cdot v(t+\tfrac{1}{2}\Delta t) \text{ (position propagation)}$$

$$v(t+\tfrac{1}{2}\Delta t) = v(t-\tfrac{1}{2}\Delta t) + \Delta t \cdot \frac{f(t)}{m} \text{ (velocity propagation)}$$

  - Velocity Verlet

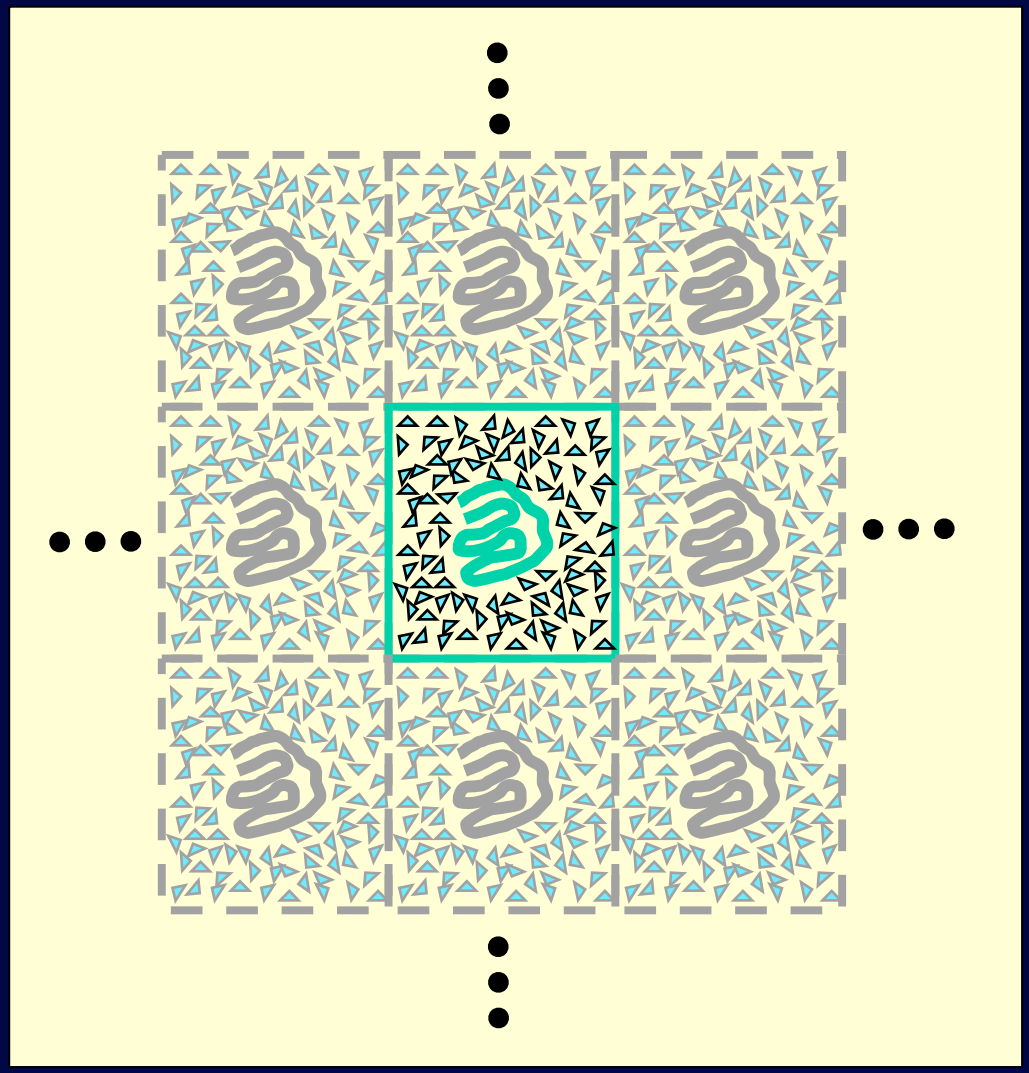
$$x(t+\Delta t) = x(t) + \Delta t \cdot v(t+\Delta t) \; \frac{1}{2m} f(t)\Delta t^2 \text{ (position propagation)}$$

$$v(t+\Delta t) = v(t) + \Delta t \cdot \frac{(f(t)+f(t+\Delta t))}{2m} \text{ (velocity propagation)}$$

- Time step controls accuracy of numerical solution
  - $\Delta t = 10^{-15}$ sec = 1 fs
  - Fundamental time step determined by high frequency vibrations (bonds)
- Highest frequency motions removed with holonomic constraints (SHAKE)
  - w/SHAKE can increase time step by ~2

Boundary Conditions and Statistical Ensembles

Periodic Boundary Conditions and Solvent Effects



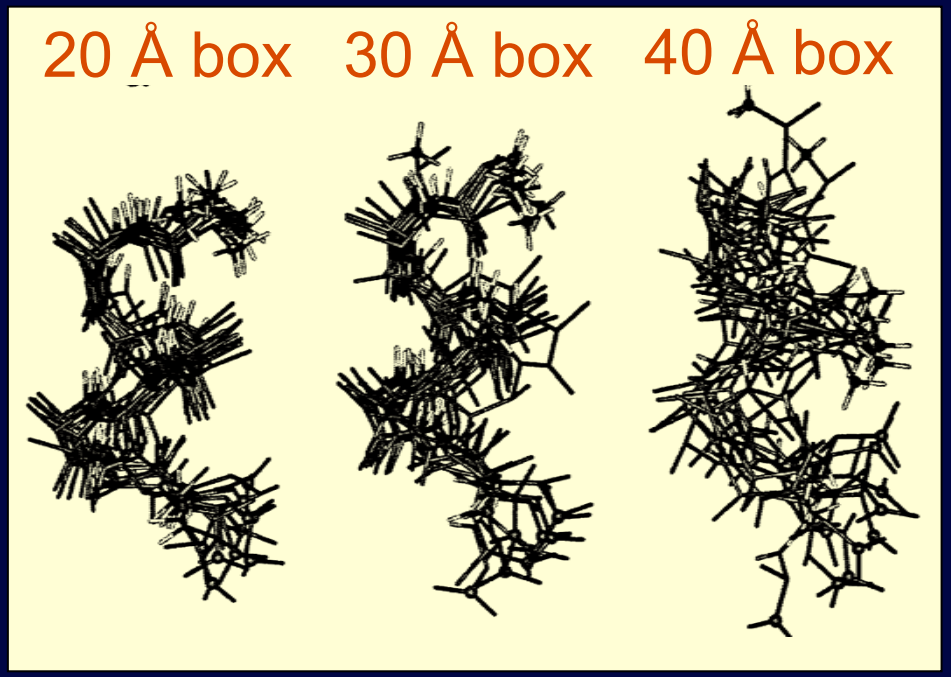
PBCs a Panacea or Not?

Hunenberger & McCammon…

- continuum calculations show artifacts
- reproduced in molecular dynamics simulations
- *J. Phys. Chem. B.* **104**, 3668-3675 (2000)

artificial stabilization of α-helix

poly-alanine octapeptide, 2 ns simulations

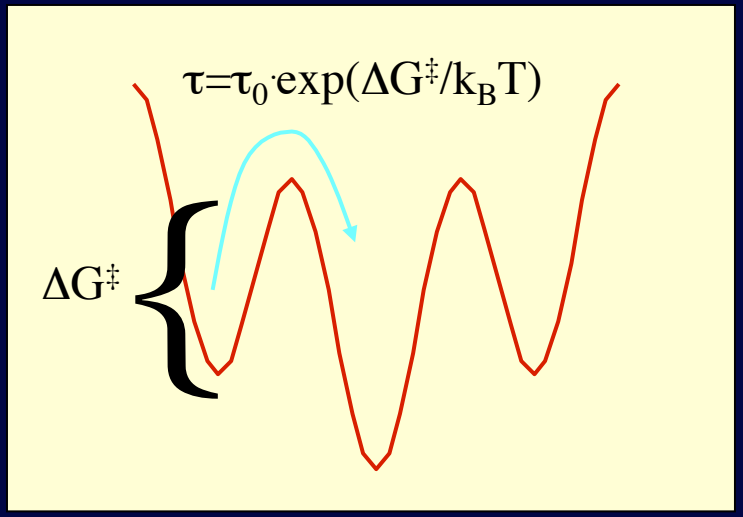


Controlling Thermodynamic Variables T and P

- Statistical ensembles connect microscopic to macroscopic/ thermodynamic
- NVE (microcanonical - Entropy rules!)
- NVT (Canonical - Helmholtz free energy is relevant, A)
  - $T=\sum m\langle v^2\rangle/(3k_B)$
- NPT (Isothermal-isobaric - Gibbs free energy is relevant, G)
  - P=kinetic + virial contributions
- Thermostats, barostats, etc., allow one to choose appropriate ensembles
  - Following Nose', Hoover, Evans and others…[see C.L. Brooks, III, Curr. Opin. Struct. Biol., **5**, 211('95)]

Barriers, Temperature and Size Yield Timescales

- How long should simulations be?



$\tau_0 \sim 10^{-12}$, $\Delta G^{\ddagger}$

1 kcal/mol: ~1.2 ps^{-1}

5 kcal/mol: ~1.5 ns^{-1}

10 kcal/mol: ms or longer!

- Sampling should exceed timescales of interest by ~10-fold

- Size and complexity also increase required timescales
  - Equilibration of ions, complex landscapes, multiple minima

Simplifications - eliminating explicit solvent and solvent boundary methods

- Free energy changes are partitioned into internal and external components
- $\Delta G_{total} = \Delta E_{internal} + \Delta S_{conformation} + \Delta G^{solvation}$
- $\Delta G^{solvation} = \Delta G^{electrostatics} + \Delta G^{H-\phi}$
- $\Delta G^{H-\phi} = \Sigma \gamma_{i*} SA_i$
- $\Delta G^{electrostatics}$ ~ continuum electrostatics