Molecular simulation and structure prediction using CHARMM and the MMTSB Tool Set

Introduction

Charles L. Brooks III

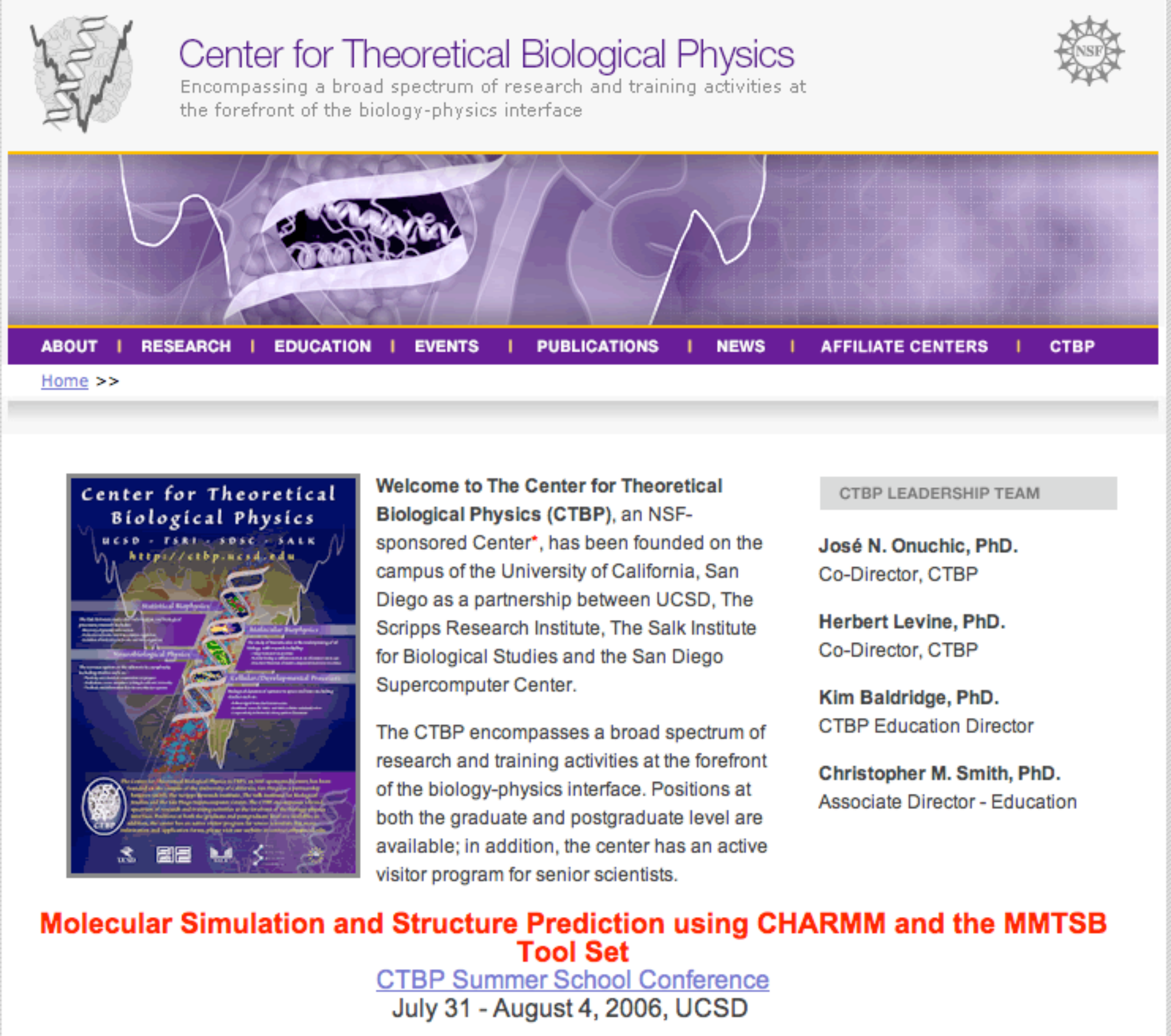
MMTSB/CTBP

2006 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, Scripps 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, David Case, Mike Holst, Terry Hwa, David Kleinfeld, Andy McCammon, Wouter Rappel, Terry Sejnowski, Wei Wang, Peter Wolynes

CTBP and MMTSB: Who are we?



Center for Theoretical Biological Physics

Encompassing a broad spectrum of research and training activities at the forefront of the biology-physics interface

Welcome to The Center for Theoretical Biological Physics (CTBP), an NSF-sponsored Center*, has been founded on the campus of the University of California, San Diego as a partnership between UCSD, The Scripps Research Institute, The Salk Institute for Biological Studies and the San Diego Supercomputer Center.

The CTBP encompasses a broad spectrum of research and training activities at the forefront of the biology-physics interface. Positions at both the graduate and postgraduate level are available; in addition, the center has an active visitor program for senior scientists.

CTBP LEADERSHIP TEAM

José N. Onuchic, PhD.
Co-Director, CTBP

Herbert Levine, PhD.
Co-Director, CTBP

Kim Baldridge, PhD.
CTBP Education Director

Christopher M. Smith, PhD.
Associate Director - Education

Molecular Simulation and Structure Prediction using CHARMM and the MMTSB Tool Set

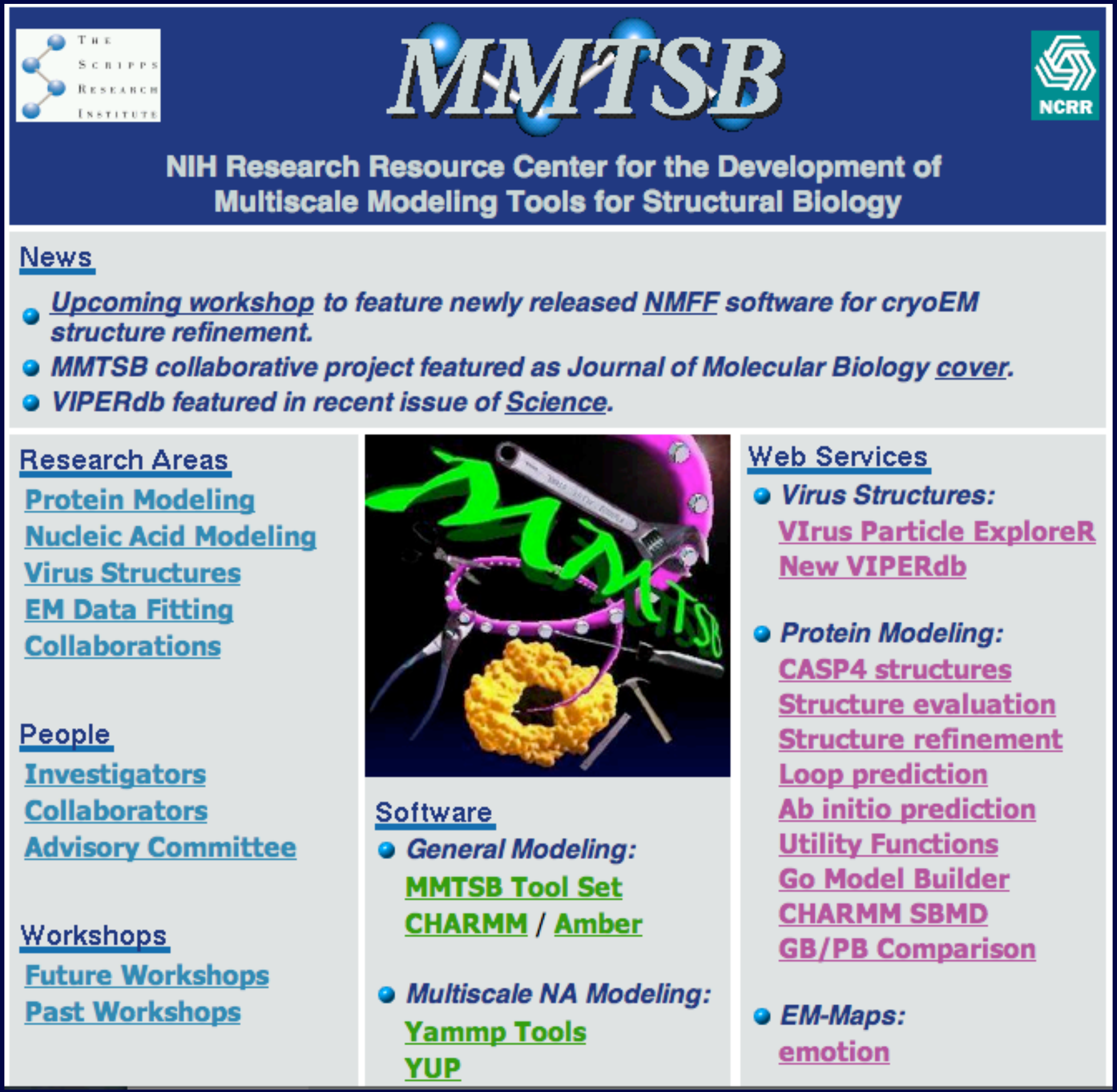
CTBP Summer School Conference
July 31 - August 4, 2006, UCSD

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 Scripps and Georgia Tech, lead by Scripps
    - 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, Steve Harvey, Jack Johnson, Vijay Reddy, Jeff Skolnick

CTBP and MMTSB: Who are we?



NIH Research Resource Center for the Development of Multiscale Modeling Tools for Structural Biology

News

- *Upcoming workshop to feature newly released NMFF software for cryoEM structure refinement.*
- *MMTSB collaborative project featured as Journal of Molecular Biology cover.*
- *VIPERdb featured in recent issue of Science.*

Research Areas

Protein Modeling
Nucleic Acid Modeling
Virus Structures
EM Data Fitting
Collaborations

People

Investigators
Collaborators
Advisory Committee

Workshops

Future Workshops
Past Workshops

Software

- *General Modeling:*
  MMTSB Tool Set
  CHARMM / Amber
- *Multiscale NA Modeling:*
  Yammp Tools
  YUP

Web Services

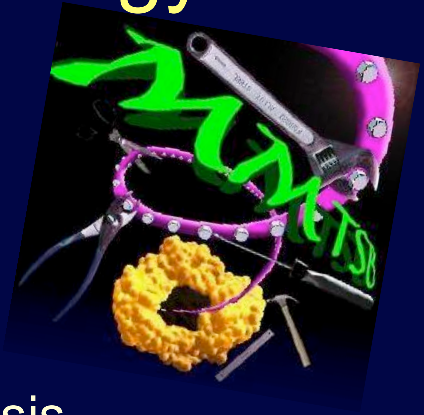
- *Virus Structures:*
  VIrus Particle ExploreR
  New VIPERdb
- *Protein Modeling:*
  CASP4 structures
  Structure evaluation
  Structure refinement
  Loop prediction
  Ab initio prediction
  Utility Functions
  Go Model Builder
  CHARMM SBMD
  GB/PB Comparison
- *EM-Maps:*
  emotion

http://mmtsb.scripps.edu

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

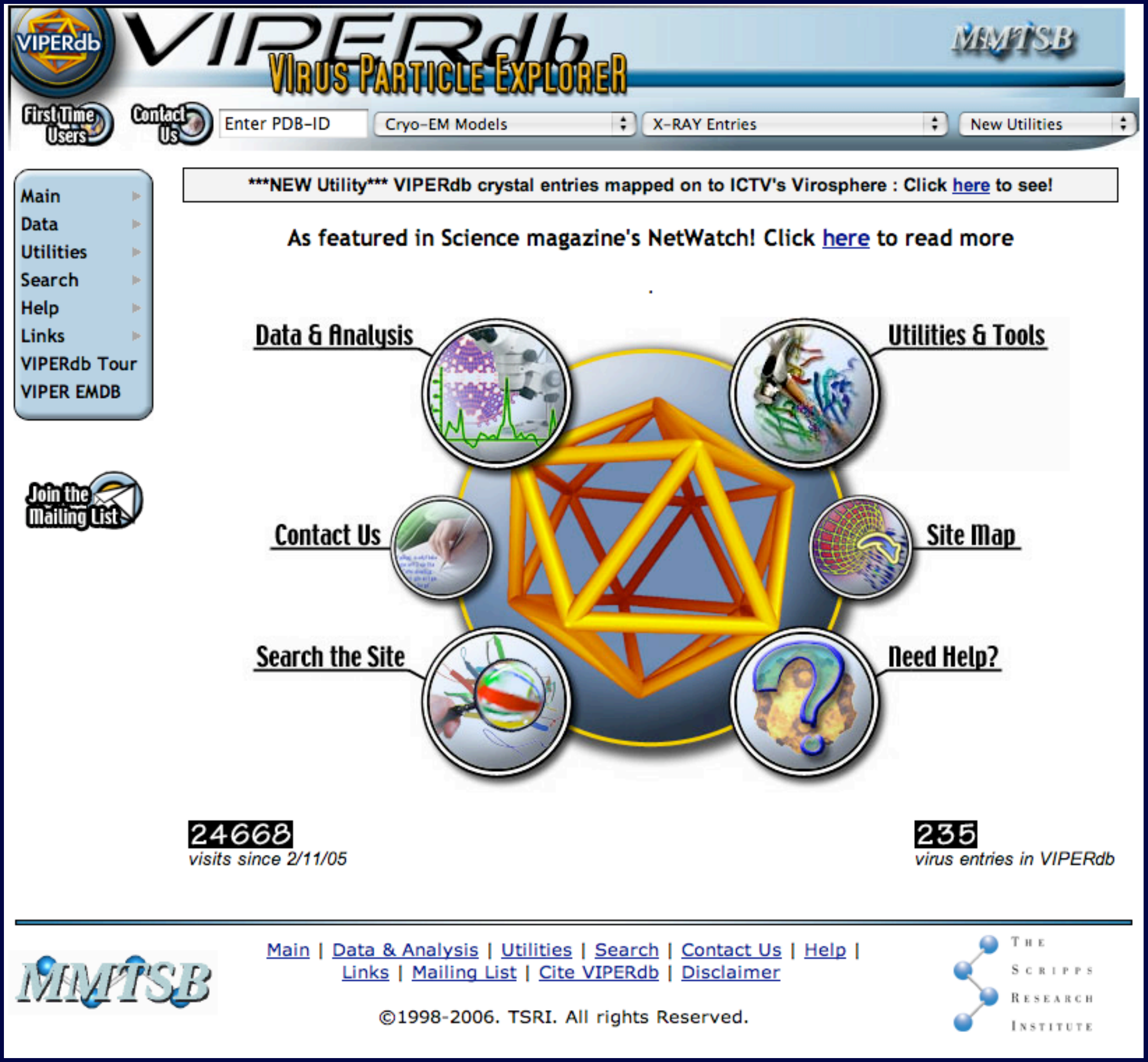
http://mmtsb.scripps.edu

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 atmic structures into electron density maps from cryo-EM and tomography

http://mmtsb.scripps.edu

Virus Particle Explorer (VIPERdb)



NEW Utility VIPERdb crystal entries mapped on to ICTV's Virosphere : Click here to see!

As featured in Science magazine's NetWatch! Click here to read more

24668
visits since 2/11/05

235
virus entries in VIPERdb

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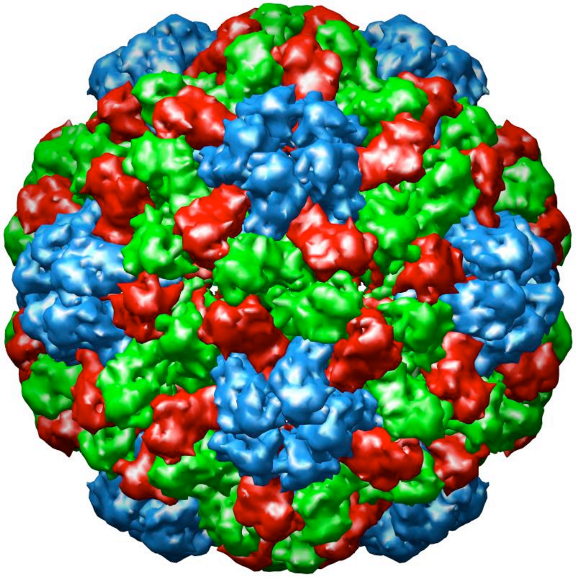


Brome Mosaic Virus

http://viperdb.scripps.edu

PREDICTOR@home

http://predictor.scripps.edu

What is Predictor@home?

Predictor@home is a world-community experiment and effort to use distributed world-wide-web volunteer resources to assemble a supercomputer able to *predict protein structure from protein sequence*. Our work is aimed at testing and evaluating new algorithms and methods of protein structure prediction. We recently performed such tests in the context of the Sixth Biannual CASP (Critical Assessment of Techniques for Protein Structure Prediction) experiment, and now need to continue this development and testing with applications to real biological targets. Our goal is to utilize these approaches together with the immense computer power that can be harnessed through the internet and volunteers all over the world (you!) to address critical biomedical questions of protein-related diseases. **Predictor@home** is a pilot project of the Berkeley Open Infrastructure for Network Computing (BOINC)

12/21/04 - An update from Professor Charles L. Brooks, III: Update

Join Predictor@Home
- Rules and policies **[read this first]**
- Getting started
- Create account
- Applications

Returning participants
- Your account - view stats, modify preferences
- Teams - create or join a team
- Download BOINC
- Add-ons

Community
- Participant profiles
- Message boards

Project totals and leader boards
- Top users
- Top hosts
- Top teams
- Other statistics

Job Opportunities
- Postdoctoral Position

Scientific Update
- Current Progress
- The Predictor@Home Model
- Results Gallery

Technology Update
- Current Progress
- The Predictor@Home Framework

About Predictor@Home
- The Predictor Plan
- The Predictor Team

Resources
- Science Links
- Technology Links
- Trouble Shooting Guide
- Predictor in the World

Statistics
- Predictor Statistics
- Server Statistics

Contacts
- Email Predictor@home

User of the Day

Witchkraft
I�m a 25 y.o. Boy from Germany....

News

06/24/06

FYI, There was a power outage Friday -> Saturday.

06/21/06

Reminder: Every Wednesday at noon pacific time we will be offline for several hours to do database backups.

05/11/06

We will be offline for a short time while we relocate the servers into a new rack.

News Archive

News is available as an RSS Feed

Current Targets

Helix H0010
Helix H0011
Helix H0012
Bovine Prion
Cyclophilin A

Supported by the NIH
Center for Multiscale Modeling Tools in Molecular Biology (MMTSB)
and the NSF
Center for Theoretical Biological Physics (CTBP)

Your instructors and mentors: Who are we?

- Charles Brooks
- Michael Feig
- Wonpil Im
- Alex MacKerell
- Lennart Nilsson
  - All biophysicists involved in MMTSB and CHARMM or MMTSB development
  - Jiannhan Chen, Mike Crowley, Jana Khandogin, Karunesh Arora
    - All biophysicists working in Brooks group as postdoctoral professional 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 provides a venue to explore documentation, discuss results and get advice from advanced CHARMM users and developers
  - Original publication: J. Comp. Chem., 4, 187 (1983)

http://www.charmm.org

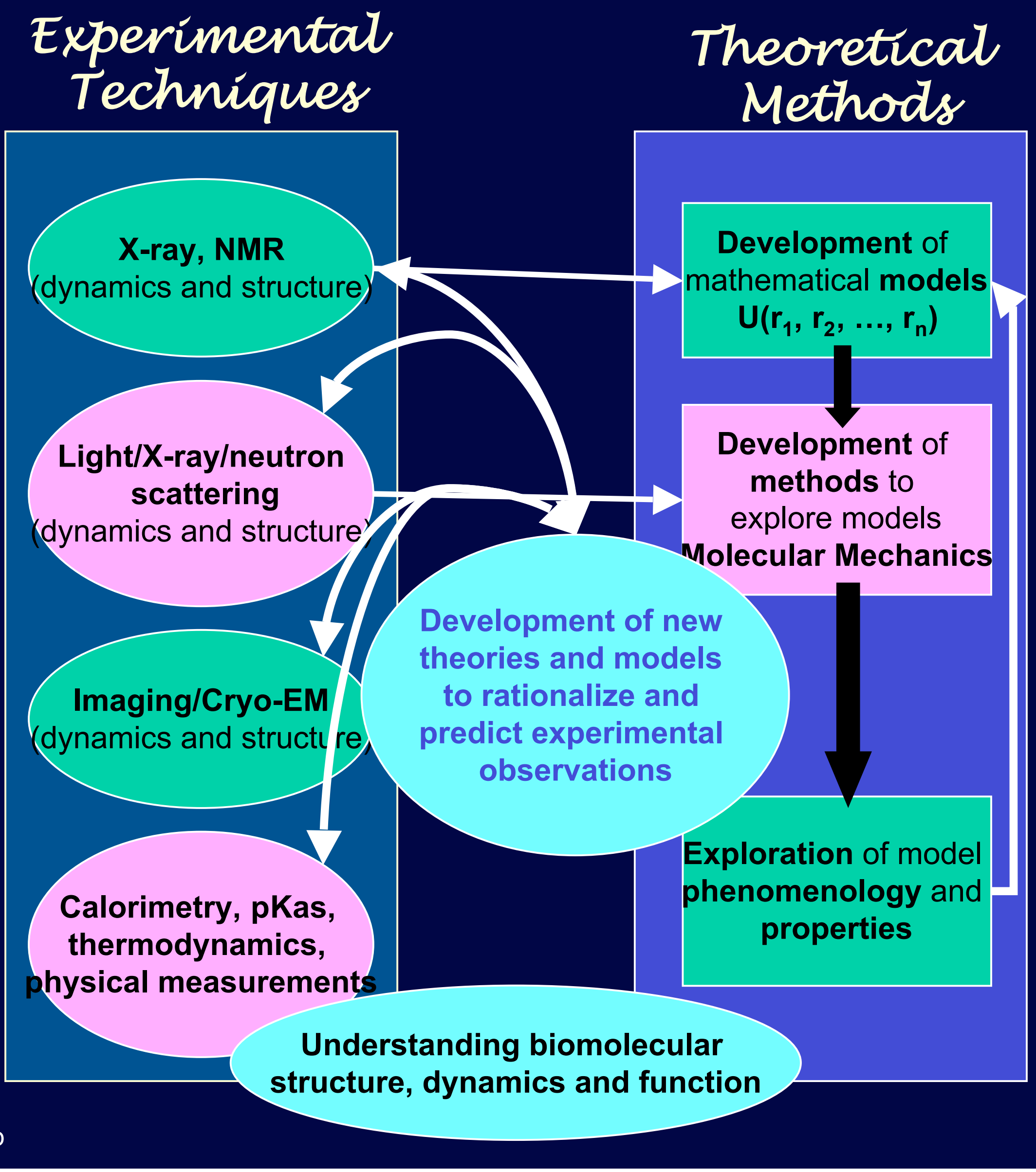
What is the MMTSB Tool Set?

- The MMTSB Tool Set is a collection of Perl-based scripts and modules that provide natural user interfaces to CHARMM, Amber, MONSSTER, MODELLER and other molecular modeling packages
  - Developed by M. Feig and J. Karanicolas in the Brooks group in 2002.
  - Currently downloaded more than 5000 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://mmtsb.scripps.edu

Molecular Mechanics and Modeling

Molecular Mechanics and Modeling - Why



Experimental Techniques

Theoretical Methods

X-ray, NMR
(dynamics and structure)

Light/X-ray/neutron scattering
(dynamics and structure)

Imaging/Cryo-EM
(dynamics and structure)

Calorimetry, pKas, thermodynamics, physical measurements

Development of mathematical **models**
$U(r_1, r_2, \ldots, r_n)$

Development of **methods** to explore models
Molecular Mechanics

Exploration of model **phenomenology** and **properties**

Development of new theories and models to rationalize and predict experimental observations

Understanding biomolecular structure, dynamics and function

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.):

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

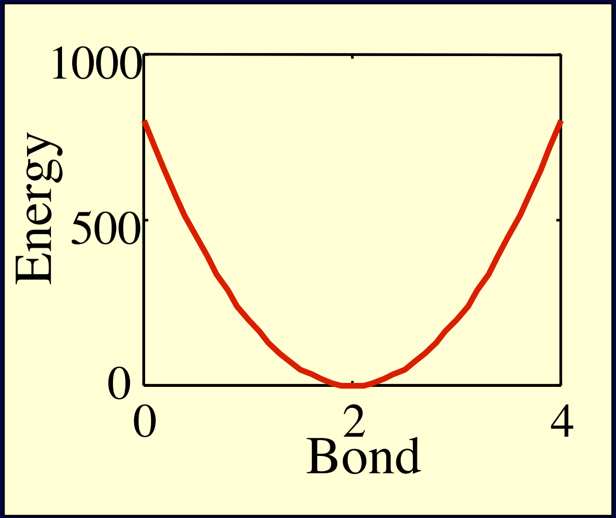
$$+ \sum_{\text{torsions, i}} k_i^\phi \cdot [1 + \cos(n_i \phi_i - \delta_i)]$$

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

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

- Energy terms - bonds

From spectroscopy, IR, etc.

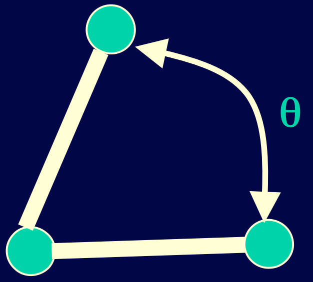


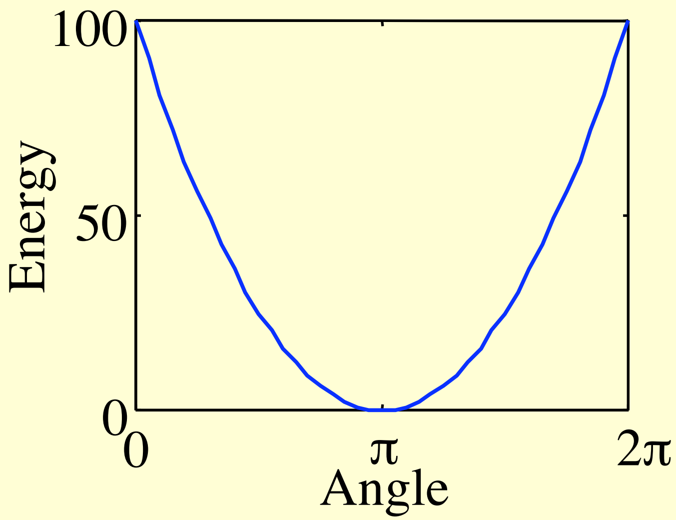
Mathematical Models - Force Fields

- Angles

From spectroscopy, IR, etc.

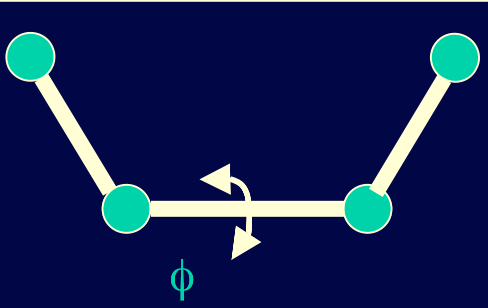
$$u_{angle} = \frac{1}{2} k_i^{\theta} \cdot (\theta_i - \theta_i^0)^2$$

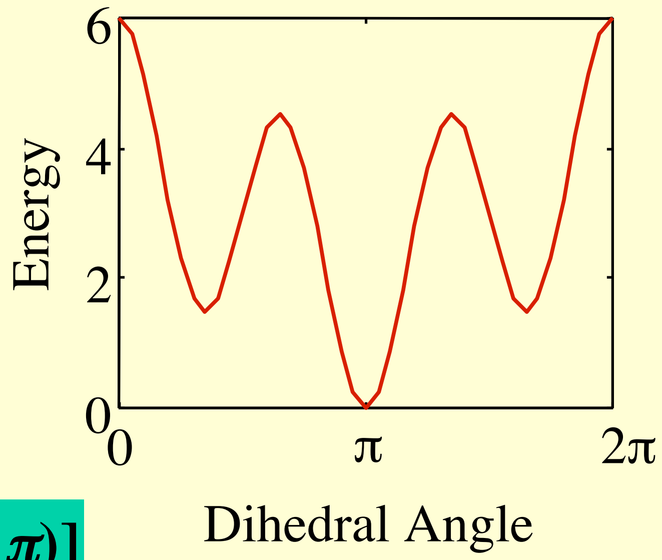




- Dihedrals

From spectroscopy, IR, NMR, empirical



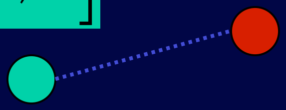


$$u_{dihedral} = k_i^{\phi} \cdot [1 + \cos(3\phi_i)] + k_i^{\phi'} \cdot [1 - \cos(\phi_i - \pi)]$$

Mathematical Models - Force Fields

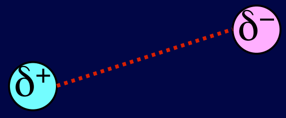
- Nonbonded - Lennard-Jones

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

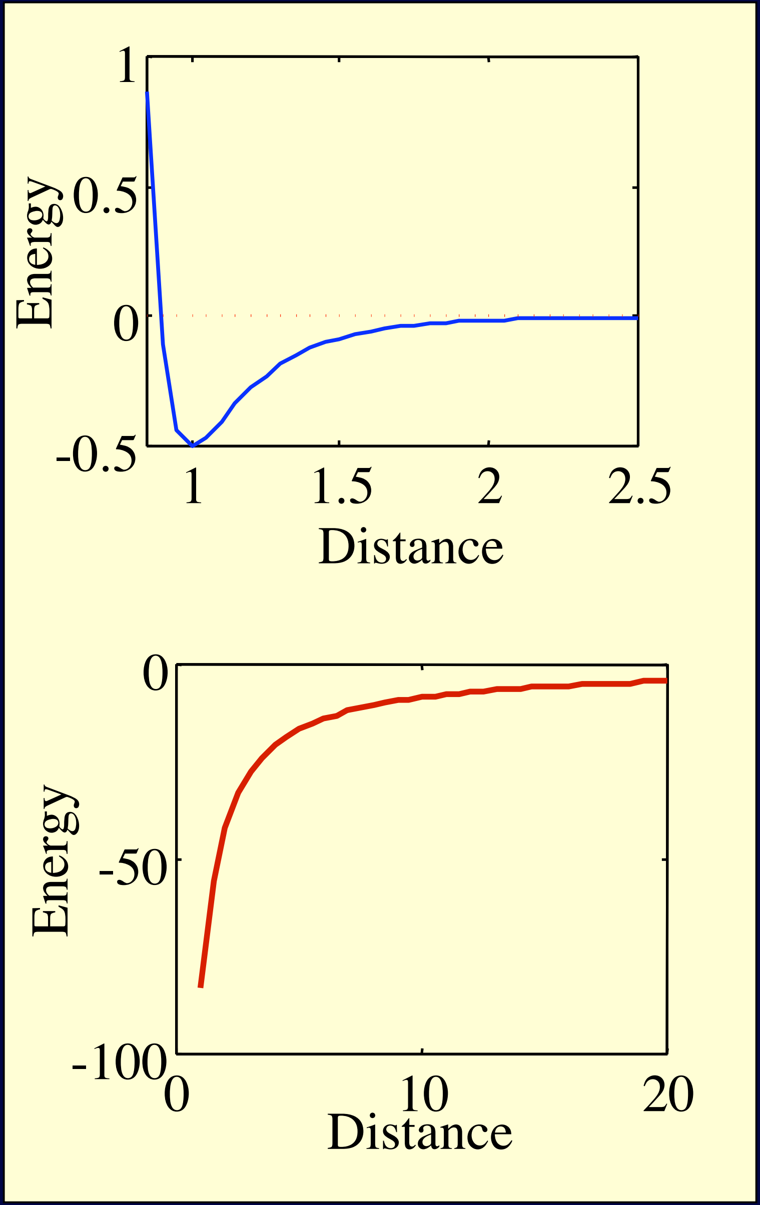


- Nonbonded - electrostatics

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



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

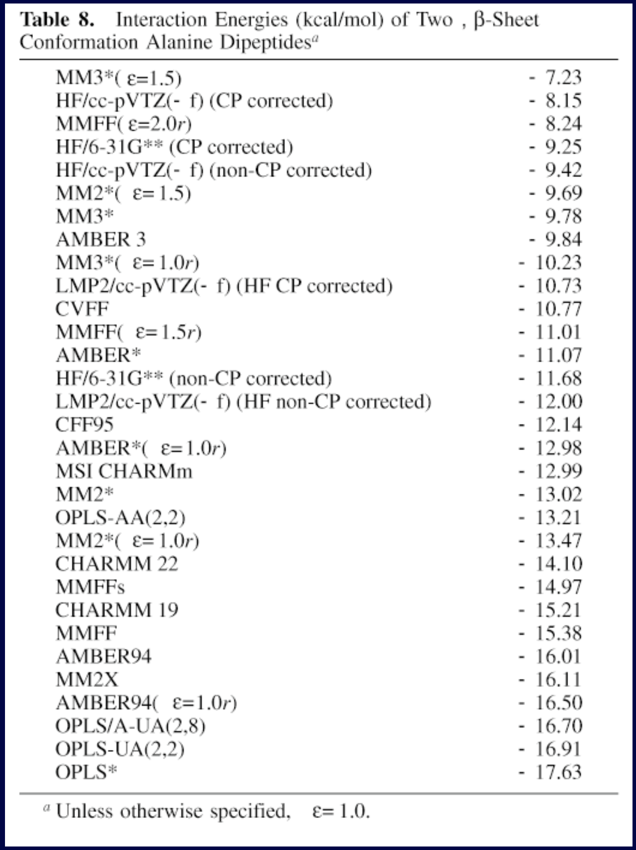
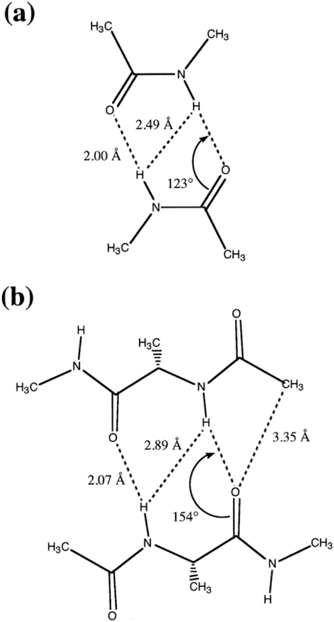
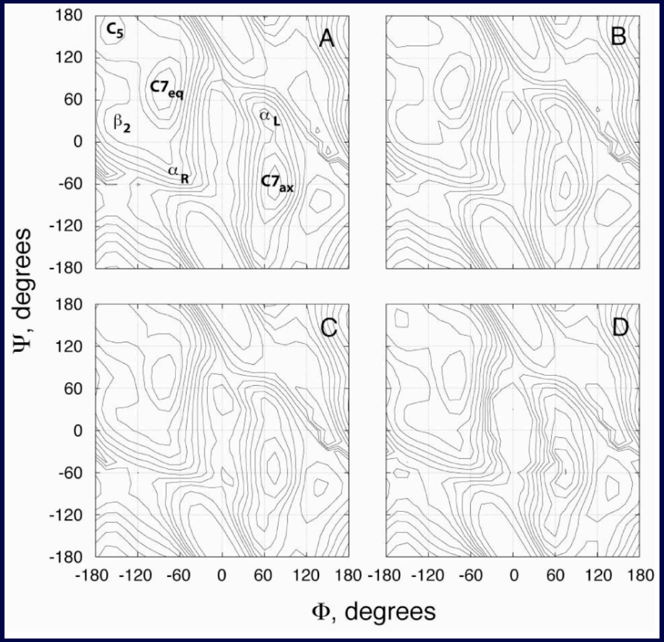


Table 8. Interaction Energies (kcal/mol) of Two , β-Sheet Conformation Alanine Dipeptides[a]

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)

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

- *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 <u>scaled</u> 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*

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

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

Total charge on molecule 'i' constant

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

average electronegativity of molecule 'i'

- *Charge Evolution/Dynamics*

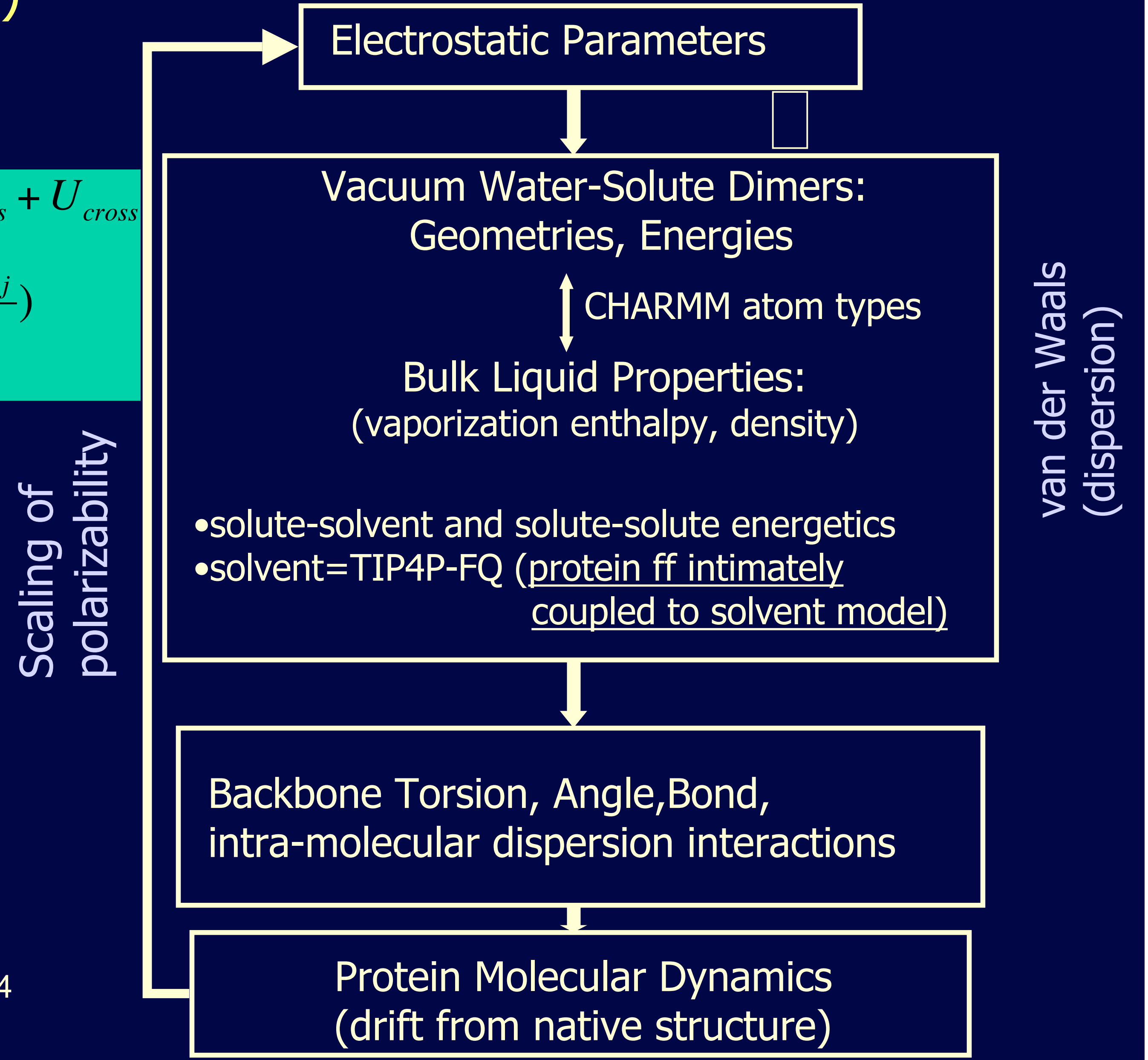
$$m_{Q,i\alpha}\ddot{Q}_{i\alpha}=-\frac{\sum_{\beta=1}^{N_i}(\tilde{\chi}_{i\alpha}-\tilde{\chi}_{i\beta})}{N_i}$$

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)

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

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



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 (<u>protein ff intimately coupled to solvent model)</u>

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

Protein Molecular Dynamics
(drift from native structure)

Scaling of polarizability

van der Waals (dispersion)

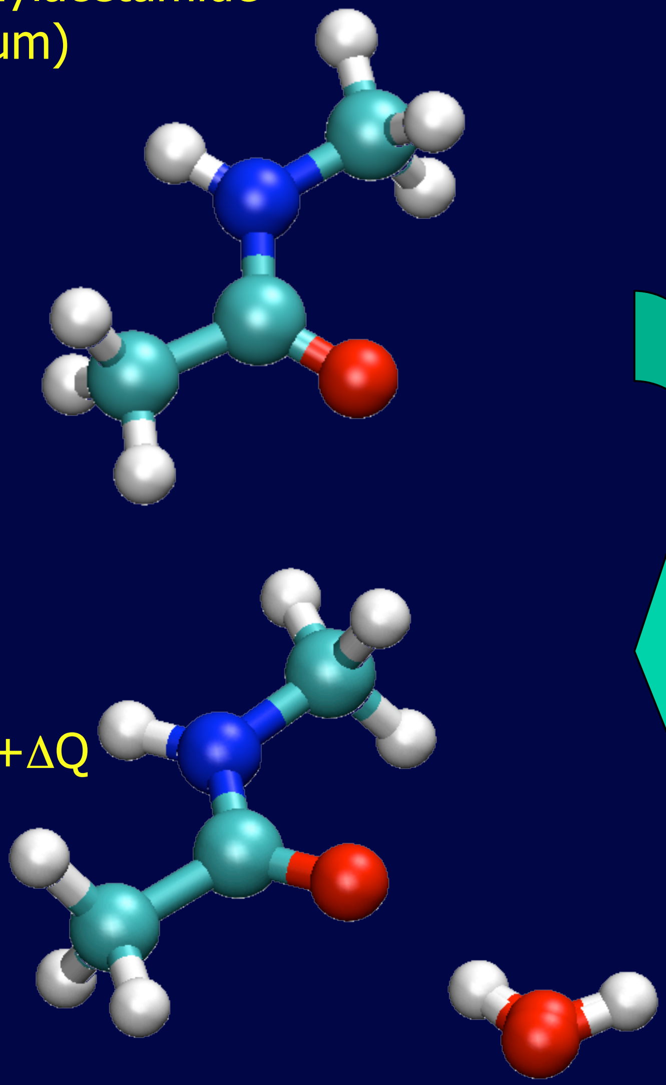
Electronic Polarization - deriving parameters

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 $\mathbf{U(x) = a/2(x\text{-}x_0)^2}$
  - 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

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

  - 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

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

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

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

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

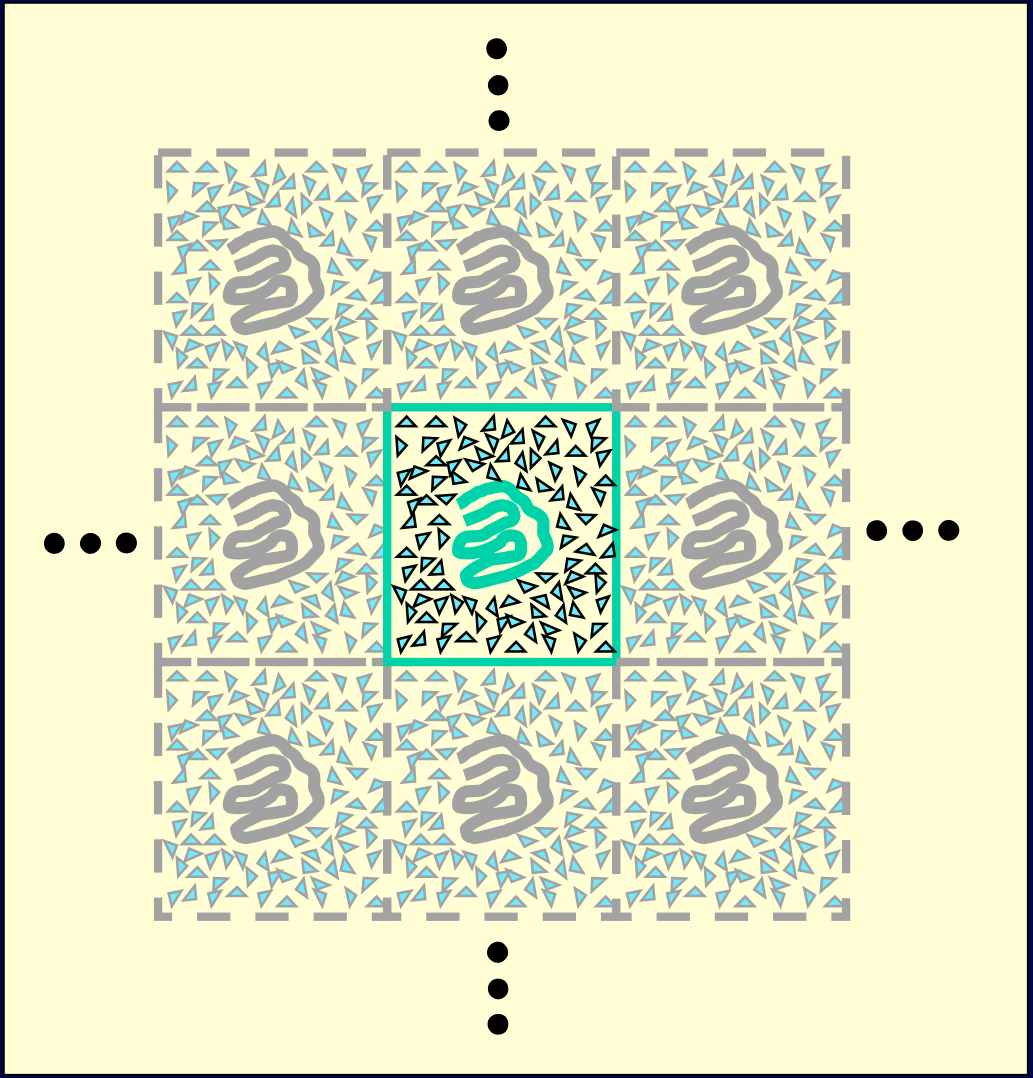
$$v(t) = (x(t + \Delta t) - x(t - \Delta t)/(2\Delta t) + O(\Delta t^3) \text{ (velocity propagation)}$$

Demystifying Molecular Mechanics - Molecular Dynamics

- Other “summed forms”
  - Leap-frog
    $$\mathrm{x}(t+\Delta t) = x(t) + \Delta t \cdot \mathrm{v}(\mathrm{t} + \tfrac{1}{2}\Delta t) \text{ (position propagation)}$$
    $$v(t+\tfrac{1}{2}\Delta t) = \mathrm{v}(\mathrm{t} - \tfrac{1}{2}\Delta t) + \Delta t \cdot \frac{f(t)}{m} \text{ (velocity propagation)}$$
  - Velocity Verlet
    $$x(t+\Delta t) = x(t) + \Delta t \cdot v(t+\Delta t) \ \ \tfrac{1}{2m} f(t)\Delta t^2 \text{ (position propagation)}$$
    $$v(t+\Delta t) = \mathrm{v(t)} + \Delta t \cdot \frac{(f(t)+f(t+\Delta t))}{2m} \text{ (velocity propagation)}$$
- Time step controls accuracy of numerical solution
  - Δt =10-15 sec = 1 fs
  - Fundamental timestep 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



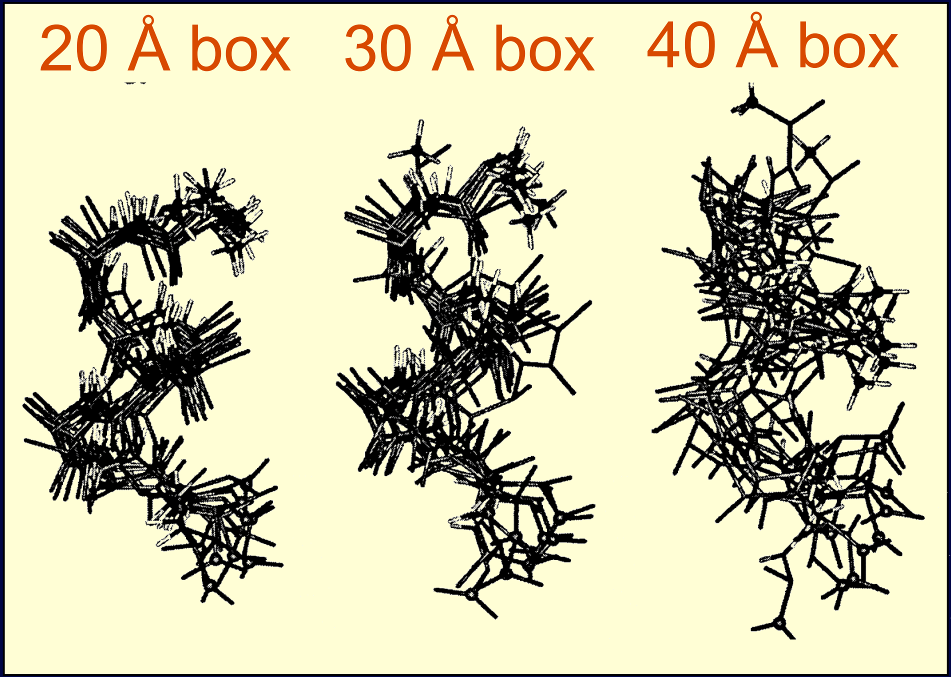
PBCs a Panacea or Not?

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

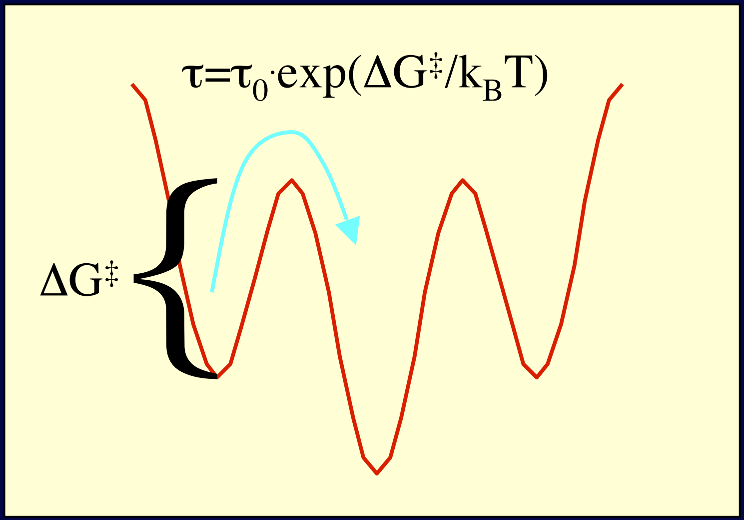


Controlling Thermodynamic Variables T and P

- 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?



$$\tau=\tau_0 \cdot \exp(\Delta G^{\ddagger}/k_BT)$$

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

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

CHARMM Simulations

The flow of data and information in a CHARMM simulation

Input

- Parameters, topologies
- Sequence, coordinates

Generate

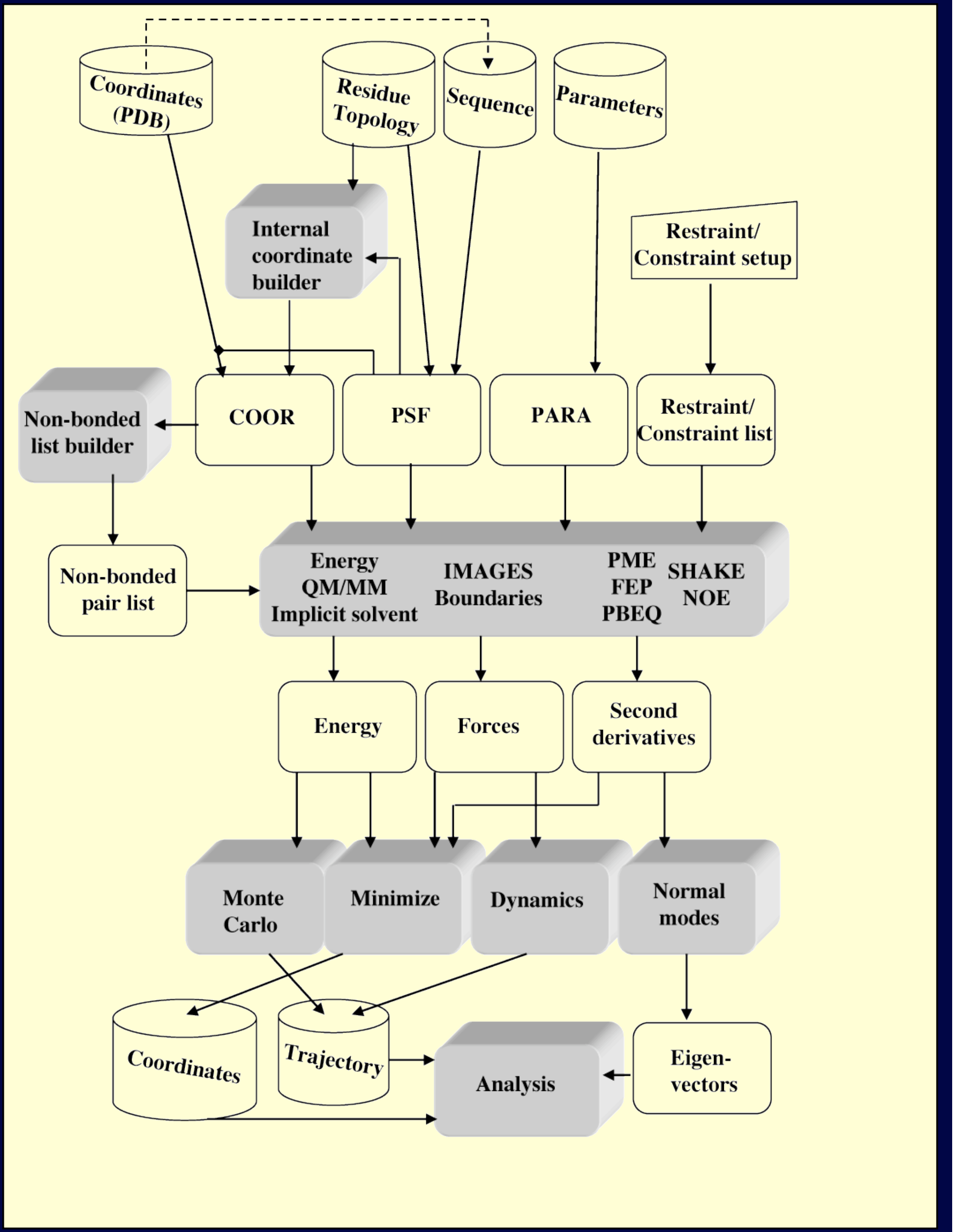
- Protein structure file
- Internal coordinates
- Missing atoms

Input

- Restraints/constraints

Calculate/Analyze

- Manipulate system
  - Energy, dynamics, normal modes, Monte Carlo, minimization
  - Analyze trajectories



Coordinates (PDB)

Residue Topology

Sequence

Parameters

Internal coordinate builder

Restraint/ Constraint setup

Non-bonded list builder

COOR

PSF

PARA

Restraint/ Constraint list

Non-bonded pair list

Energy QM/MM Implicit solvent

IMAGES Boundaries

PME FEP PBEQ

SHAKE NOE

Energy

Forces

Second derivatives

Monte Carlo

Minimize

Dynamics

Normal modes

Coordinates

Trajectory

Analysis

Eigen-vectors

The scope and range of methodologies and systems studied with CHARMM

Simulation methodologies

- Classical force field methods
  - Minimization, molecular dynamics, Langevin dynamics, Monte Carlo, normal mode calculations
- Quantum and QM/MM
  - Internal semi-empirical AM1/PM3 and DFFTB methods
  - Interfaces with numerous QM packages
- Sampling methods
  - Umbrella sampling
  - FEP/TI
  - Path and NEB (string of states methods)
  - Multi-canonical and replica approaches

Force fields and systems

- All atom force fields w/ (for proteins and lipids) and w/o atomic polarization
- Extended (polar hydrogen only) force fields
- Many coarse-grained, multi-resolution representations are feasible