# Lecture 7: Advanced Topics in MM & MS

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# Project 2: MD Simulations

1. Select a protein system

| Protein Class | PDB Code | -log$k_d$ | Resolution |
|---|---|---|---|
| Neuraminidase | 2QWG | 8.4 | 1.8 |
| DHFR | 1DHF | 7.4 | 2.3 |
| L-arabinose | 1ABE | 6.52 | 1.7 |
| Thrombin | 1A5G | 10.15 | 2.06 |
| Human oxresin receptor 1 | 4ZJ8 | ~10 | 2.75 |

# Project 2 MD Simulations -Continued

2. Select top hits from autodock-vina screening
   - Top 2 and bottom 1

3. Prepare ligand structures and residue topologies
   - Add hydrogen with adt
   - Generate Gaussian gcrt file with antechamber
   - Run G09 to calculate electrostatic potentials (ESP)
   - Run Antechamber to assign RESP charges
   - An alternative is run antechamber to assign am1-bcc charge

# Project 2 MD Simulations -Continued

4. Prepare topology files for minimization and MD simulations
   - xleap
   - tleap

5. Run Minimization and MD simulations using a delicate scheme
   - Minimization with main chain restrained using a set of gradually reduced restraint force constants
   - MD simulation with main chain restrained using a set of gradually reduced restraint force constants
   - Heat systems up using a set of temperatures
   - Equilibrium phase
   - Sampling phase

# Project 2 MD Simulations -Continued

6. Analyze MD snapshots
    - Average structure
    - RMSD ~ simulation time plots
    - Quasi-harmonic analysis
    - MD movie

# Project 3: Binding Free Energy Calculations With MM-PB/GBSA

1. Select a protein system

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| Neuraminidase | 2QWG | 8.4 | 1.8 |
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# Project 3: Binding Free Energy Calculations With MM-PB/GBSA

2. Prepare topologies for energy calculations with implicit solvent
   - Xleap
   - Tleap

3. Run mmpbsa.py to do the calculation
   - Input file
   - Output files

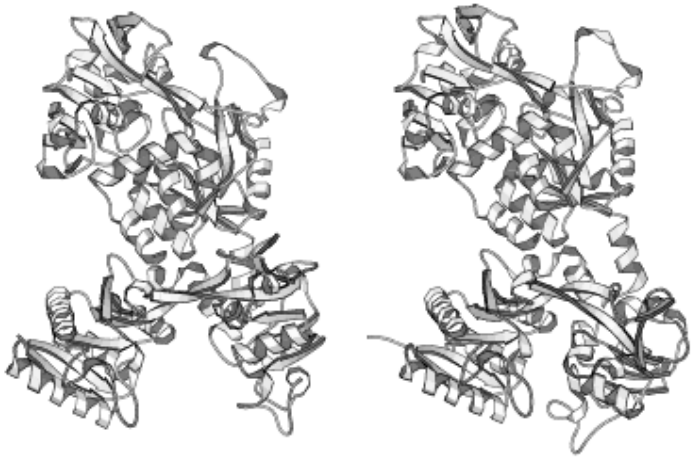
4. Analyze the MM-PB/GBSA results

# Frequency Analysis

# Frequency Analysis: low-frequency modes important for proteins

Normal mode analysis (NMA) is a powerful tool for predicting the possible movements of a given macromolecule. It has been shown recently that half of the known protein movements can be modelled by using at most two low-frequency normal modes.

Applications of NMA cover wide areas of structural biology, such as the study of protein conformational changes upon ligand binding, membrane channel opening and closure, potential movements of the ribosome,and viral capsid maturation.

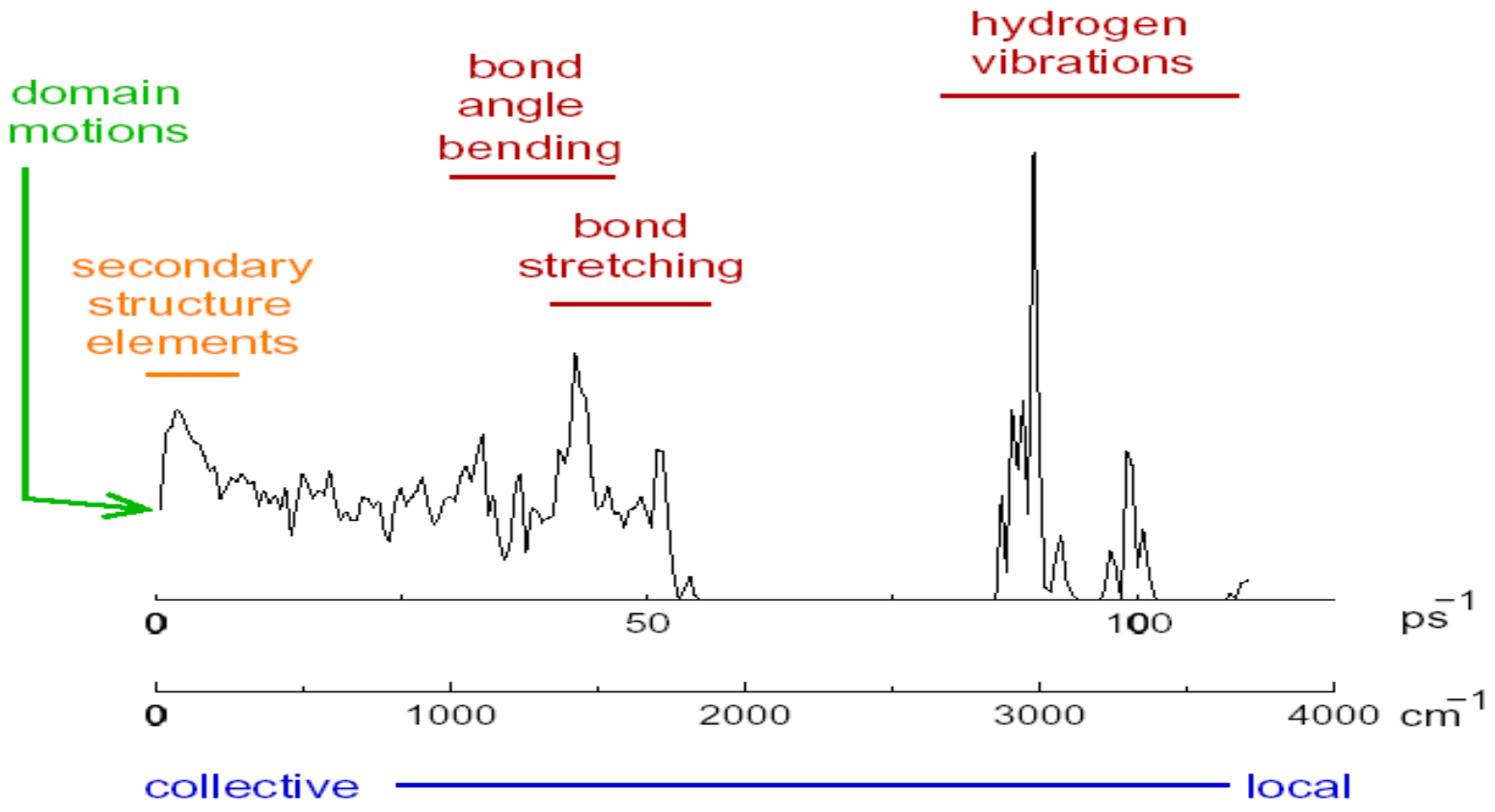


apo (left) and holo (right) forms of lactoferrin

High frequency modes are usually localized – a bond stretch for example, and are not important. Low frequency modes are usually delocalized (eg. breathing modes)

http://www.igs.cnrs-mrs.fr/elnemo/examples.html

# Protein flexibility



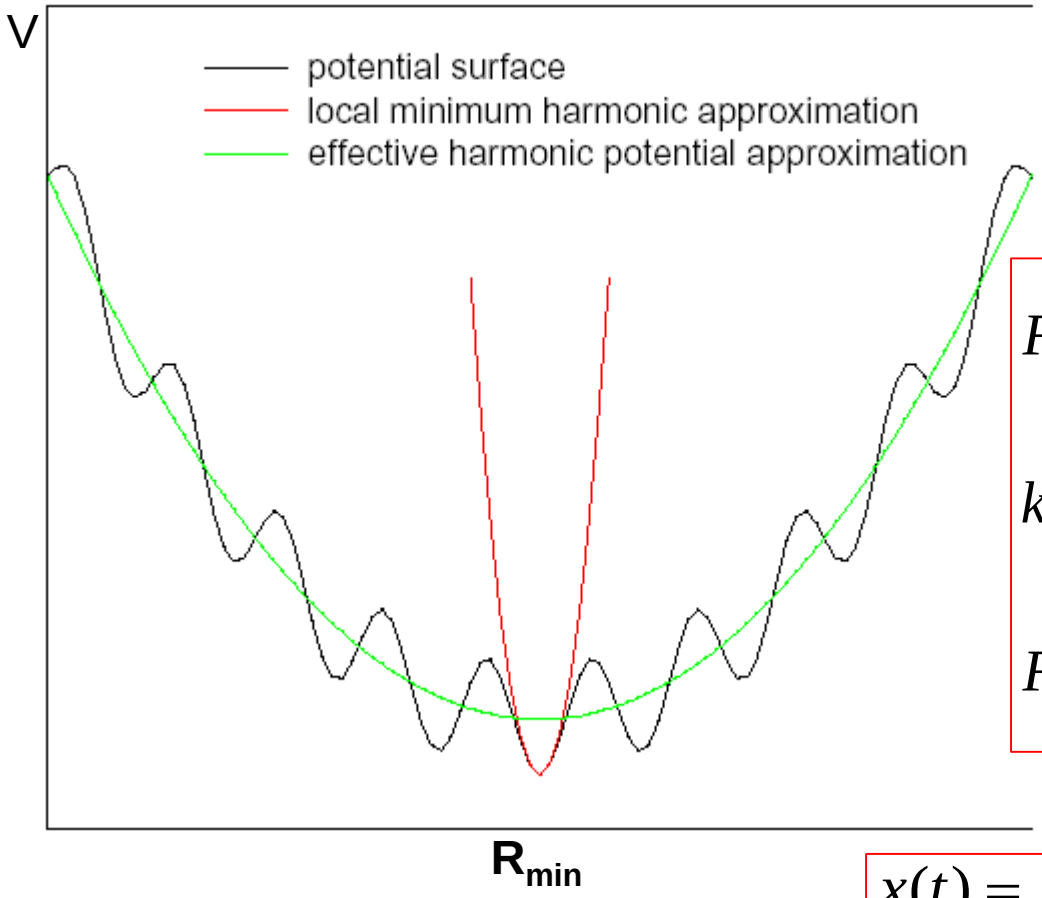
# How to Do Frequency Analysis

- Using minimization to obtain starting conformation, and computing the Hessian K:
  - Vibrational NMA
- Given starting structure:
  - Coarse grained models
- Elastic network model
- C. Given set of conformations corresponding to the motion of the molecule:
  - Essential dynamics

# Comparison chart

| | Amplitude | Time scale | Starting structure | Practical |
|---|---|---|---|---|
| Vibrational | Small | Short | By Minimization | Y/N |
| Brownian | Large | Long | By Minimization | Y/N |
| Coarse grained | Large | Long | Given | Y |
| Elastic network model | Large | Long | Given | Y |
| Essential | Large | Long | Given | Y/N |

# Harmonic approximation




$$F = -\frac{dV}{dx} = -kx \quad \rightarrow \quad V = \frac{1}{2}kx^2$$

$$k = \frac{d^2V}{dx^2}$$

$$F = ma \quad m\frac{d^2x}{dt^2} = -kx$$

$$x(t) = A\sin(2\pi\nu t)$$

$$-m(2\pi\nu)^2 A\sin(2\pi\nu t) = -kx$$

$$(2\pi\nu)^2 = k/m \Rightarrow \nu = \frac{1}{2\pi}\sqrt{\frac{k}{m}}$$

# Basic Procedure of NMA

- Minimization
  - Conjugated gradient
  - Newton Raphson
- Construct Hessian matrix (Eq. 2)
- Construct mass-weighted force constant matrix F (Eq. 3)
- Solve secular equation (Eq. 4)

$$H_{ij}(f) = \frac{\partial^2 f}{\partial x_i \partial x_j} \quad (1)$$

$$H(f) = \begin{bmatrix} \frac{\partial^2 f}{\partial x_1^2} & \frac{\partial^2 f}{\partial x_1 \partial x_2} & \cdots & \frac{\partial^2 f}{\partial x_1 \partial x_n} \\ \frac{\partial^2 f}{\partial x_2 \partial x_1} & \frac{\partial^2 f}{\partial x_2^2} & \cdots & \frac{\partial^2 f}{\partial x_2 \partial x_n} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial^2 f}{\partial x_n \partial x_1} & \frac{\partial^2 f}{\partial x_n \partial x_2} & \cdots & \frac{\partial^2 f}{\partial x_n^2} \end{bmatrix} \quad (2)$$

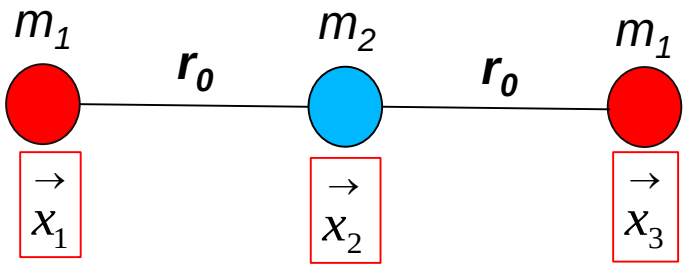
$$F = M^{-1/2} H M^{-1/2} \quad (3)$$

$$FA = \lambda A \quad (4)$$

$$\nu_i = \frac{\sqrt{\lambda_i}}{2\pi} \quad (5)$$

λ: eigenvalues, used to determine vibrational frequencies (Eq. 5)
A: eigenvectors, correspond to the amplitudes (A) of each normal mode

# Example: $CO_2$




$$f = \frac{1}{2}k(x_1 - x_2)^2 + \frac{1}{2}k(x_2 - x_3)^2 \quad (1)$$

$$\frac{\partial f}{\partial x_1} = k(x_1 - x_2) \quad \frac{\partial f}{\partial x_2} = -k(x_1 - x_2) + k(x_2 - x_3) \quad \frac{\partial f}{\partial x_3} = -k(x_2 - x_3) \quad (2)$$

$$H(f) = \begin{bmatrix} k & -k & 0 \\ -k & 2k & -k \\ 0 & -k & k \end{bmatrix} \quad (3)$$

$$F = M^{-1/2} H M^{-1/2} \quad (4) \quad M = \begin{bmatrix} m_1 & 0 & 0 \\ 0 & m_2 & 0 \\ 0 & 0 & m_1 \end{bmatrix} \quad (5)$$

# Example: $CO_2$ -Continued

$$F = \begin{bmatrix} \frac{k}{m_1} & -\frac{k}{\sqrt{m_1 m_2}} & 0 \\ -\frac{k}{\sqrt{m_1 m_2}} & \frac{2k}{m_1} & -\frac{k}{\sqrt{m_1 m_2}} \\ 0 & -\frac{k}{\sqrt{m_1 m_2}} & \frac{k}{m_1} \end{bmatrix} \quad (6)$$

$$F - I\lambda = \begin{bmatrix} \frac{k}{m_1} - \lambda & -\frac{k}{\sqrt{m_1 m_2}} & 0 \\ -\frac{k}{\sqrt{m_1 m_2}} & \frac{2k}{m_1} - \lambda & -\frac{k}{\sqrt{m_1 m_2}} \\ 0 & -\frac{k}{\sqrt{m_1 m_2}} & \frac{k}{m_1} - \lambda \end{bmatrix} \quad (7)$$

$$\begin{bmatrix} \frac{k}{m_1} - \lambda & -\frac{k}{\sqrt{m_1 m_2}} & 0 \\ -\frac{k}{\sqrt{m_1 m_2}} & \frac{2k}{m_1} - \lambda & -\frac{k}{\sqrt{m_1 m_2}} \\ 0 & -\frac{k}{\sqrt{m_1 m_2}} & \frac{k}{m_1} - \lambda \end{bmatrix} \begin{pmatrix} A_1 \\ A_2 \\ A_3 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix} \quad (7)$$

# Example: $CO_2$ -Continued

$$\lambda = \frac{k}{m_1}: \quad A_1 = -A_3, \quad A_2 = 0$$

$$\lambda = 0: \quad A_1 = A_3, \quad A_2 = \sqrt{\frac{m_2}{m_1}} A_1$$

$$\lambda = k\frac{m_2 + 2m_1}{m_1 m_2}: \quad A_1 = A_3, \quad A_2 = -2\sqrt{\frac{m_1}{m_2}} A_1$$

**For $\lambda = k/m_1$,**

$$\begin{bmatrix} \frac{k}{m_1} - \lambda & -\frac{k}{\sqrt{m_1 m_2}} & 0 \\ -\frac{k}{\sqrt{m_1 m_2}} & \frac{2k}{m_1} - \lambda & -\frac{k}{\sqrt{m_1 m_2}} \\ 0 & -\frac{k}{\sqrt{m_1 m_2}} & \frac{k}{m_1} - \lambda \end{bmatrix} \begin{pmatrix} A_1 \\ A_2 \\ A_3 \end{pmatrix} \rightarrow \begin{array}{r} -\frac{k}{\sqrt{m_1 m_2}} A_2 = 0 \\ -\frac{k}{\sqrt{m_1 m_2}} A_1 - \frac{k}{\sqrt{m_1 m_2}} A_3 = 0 \\ -\frac{k}{\sqrt{m_1 m_2}} A_2 = 0 \end{array}$$

$$A_1^2 + A_2^2 + A_3^2 = 1$$

$A_1$ = -0.707108
$A_2$ = 0
$A_3$ = 0.707108

# Example: $CO_2$ -Continued

$$\lambda_1 = 0$$

$$\lambda_2 = \frac{k}{m_1}$$

$$\lambda_3 = k\frac{m_2 + 2m_1}{m_1 m_2}$$

$k$ = 1600 $Nm^{-1}$
$m_1$ = 16
$m_2$ = 12

$$\nu_1 = \frac{\sqrt{\lambda}}{2\pi} = \frac{\sqrt{0}}{2\pi} = 0$$

$$\nu_2 = \frac{\sqrt{\lambda}}{2\pi} = c\frac{\sqrt{1600/16}}{2\pi} = 818.57 \times 10/2/3.1415926 = 1302\ cm^{-1}$$

$$\nu_3 = \frac{\sqrt{\lambda}}{2\pi} = c\frac{\sqrt{1600 \times (12+16\times 2)/12/16}}{2\pi} = 818.57 \times 19.148/2/3.1415926 = 2494.6\ cm^{-1}$$

$$c = \frac{\sqrt{1000 \times N_A}}{100 \times 2.9979 \times 10^8} = 818.57$$

*c*: Conversion factor

**Expt**: 667, 667, 1340 and 2349 $cm^{-1}$

# Normal Mode Analysis: PSD95 PDZ

- Input file using the nab program

  *Sample input*

  *nab –o nma nma.nab*

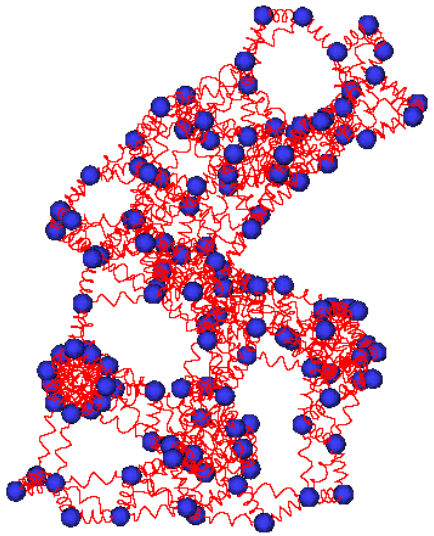
- Output file

  Sample output

- PSD95 PDZ domain: 120 AA, 1821 atoms

# Coarse grained models

- **Capture collective motions**
  - Specific to a protein
  - Usually related to its function
  - Largest amplitudes
- Atoms are point masses
- Springs between nearby points



# Elastic Network Model

$$\Delta r_i = r_i - r_i^0 \qquad \Delta r_j = r_j - r_j^0$$

$$\Delta r_{ij} = \Delta r_j - \Delta r_i = r_{ij} - r_{ij}^0$$

$$V = \frac{\gamma}{2}\sum_{i,j}^{N}\left(r_{ij} - r_{ij}^0\right)^2 = \frac{\gamma}{2}\sum_{i,j}^{N}\left(\Delta r_i \Gamma_{ij} \Delta r_j\right)$$

$$\Gamma_{ij} = \begin{cases} -1, & if\ i \neq j\ and\ r_{ij} \leq r_c \\ 0, & if\ i \neq j\ and\ r_{ij} > r_c \\ -\sum_{j, i \neq j}^{N} \Gamma_{ij}, & if\ i = j \end{cases}$$

$r_i$ *and* $r_j$*: position vectors*
$r_i^0$ *and* $r_j^0$*: equilibrium position vectors*
$r_{ij}$*: distance vector*

$\Delta r_i$ *and* $\Delta r_j$ *: instantaneous fluctuation position vectors*
$\Delta r_{ij}$ *: instantaneous fluctuation distance vectors*

$F_{ij}$*: inter-node contact matrix*

$\gamma$: force constant for the elastic bond between any two bonded atoms

$r_c$: cutoff, 7.0-7.5 Å

# Elastic Network Model

$$\Delta r_i = r_i - r_i^0 \qquad \Delta r_j = r_j - r_j^0$$

$$\Delta r_{ij} = \Delta r_j - \Delta r_i = r_{ij} - r_{ij}^0$$

$$c_{ij} = \left\langle \Delta r_i \Delta r_j \right\rangle / \left[ \left\langle (\Delta r_i)^2 (\Delta r_j)^2 \right\rangle \right]^{\frac{1}{2}}$$

$$= [\Gamma^{-1}]_{ij} / ([\Gamma^{-1}]_{ii} [\Gamma^{-1}]_{jj})^{\frac{1}{2}}$$

$$\Gamma^{-1} = \frac{3k_B T}{\gamma} \sum_k \lambda_k^{-1} \mu_k \mu_k^T$$

$$[C]_k = \lambda_k^{-1} \mu_k \mu_k^T$$

$C_{ij}$ : correlation between Nodes *i* and *j*

*$[C]_k$: contribution of Mode k to the correlation*

# Gaussian Elastic Network Model

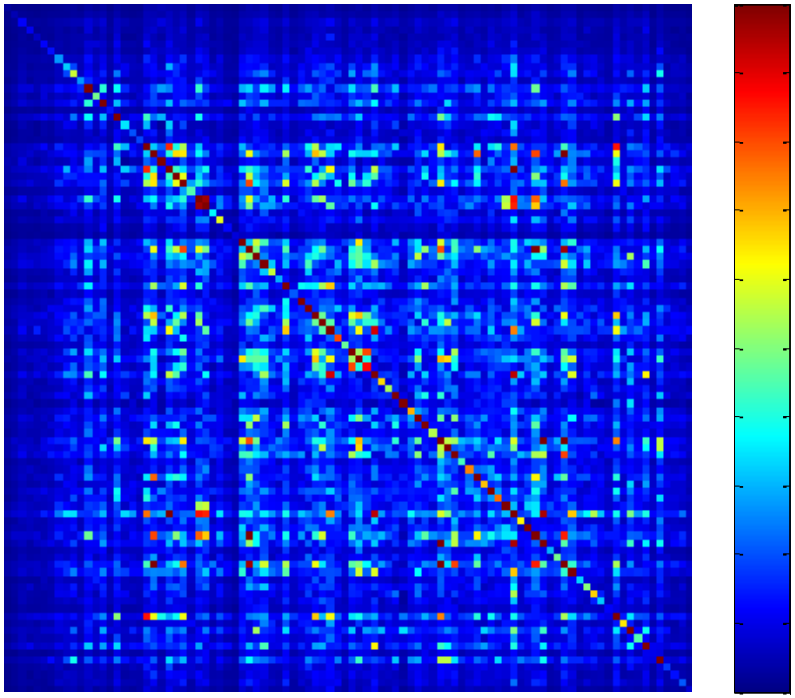
iGNM: http://ignm.ccbb.pitt.edu/

oGNM: http://gnm.csb.pitt.edu/

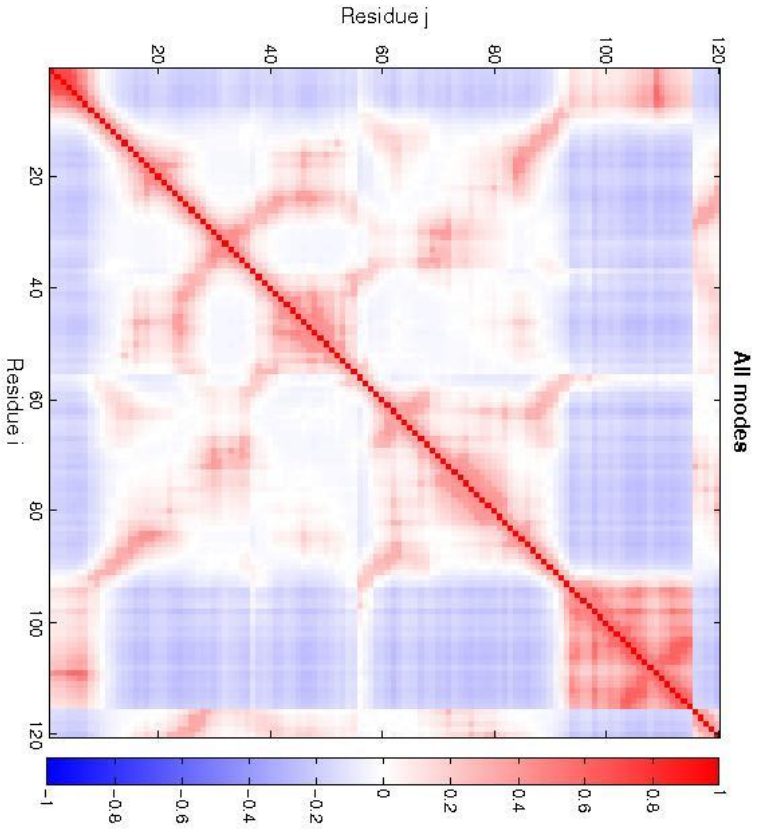
Developed by Ivet Bahar at University of Pittsburgh

# Correlation Matrix Identified by Statistical Coupling Analysis (SCA)

PDZ, 240 Sequences



SCA




iGNM

# Essential dynamics

- Given a set of structures that reflect the flexibility of the molecule
- Find the coordinates that contribute significantly to the fluctuations
- time scale: >> residence time in a minimum

$$C = \left\langle (x(t) - < x >)((x(t) - < x >)^T \right\rangle$$

$$C = T \Lambda T^T$$

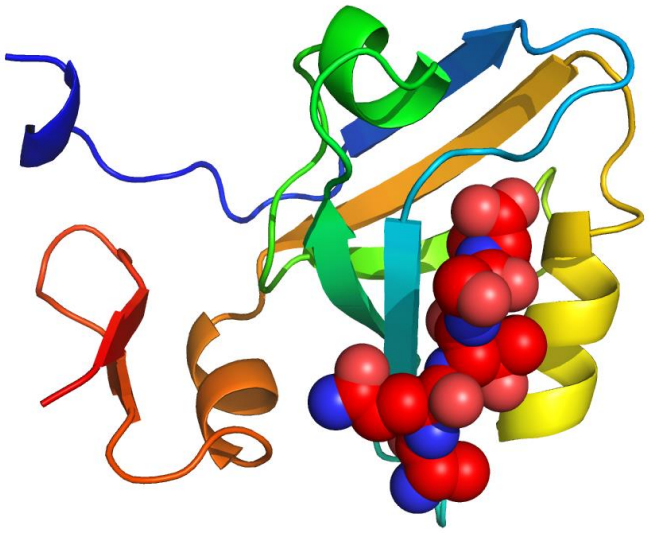
- Quasi-harmonic analysis

$$y = M^{\frac{1}{2}} x$$

$$C = \left\langle (y(t) - < y >)((y(t) - < y >)^T \right\rangle$$

$$C = T \Lambda T^T$$

# Quasi-Harmonic Analysis: PSD95 PDZ



- Input file for ptraj quasi-harmonic analysis

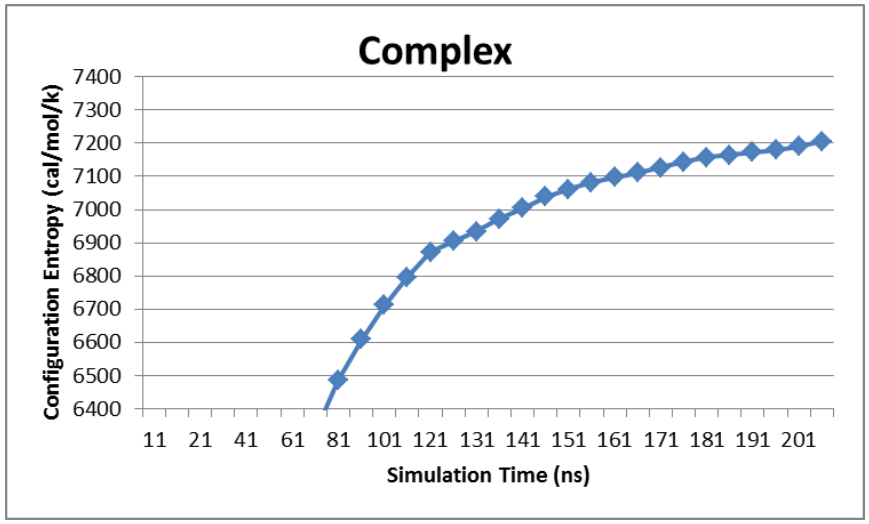
  *Sample input*

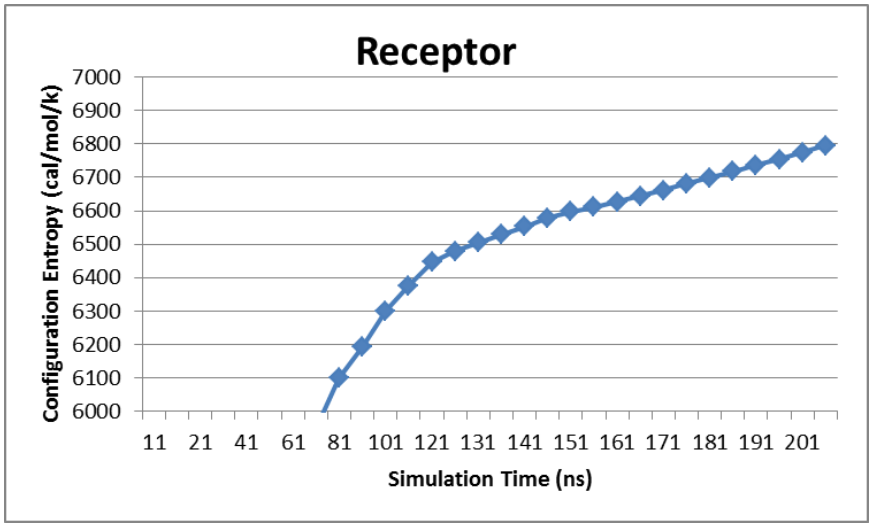
- Output file

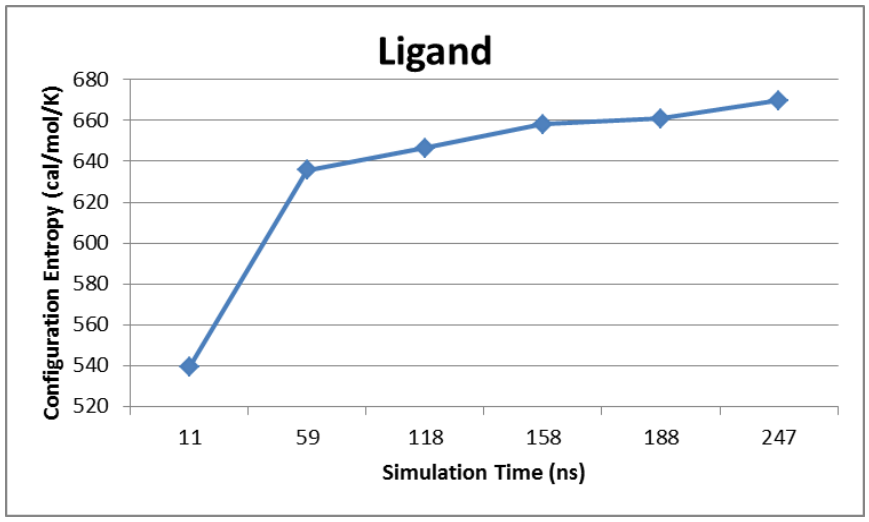
  Sample output

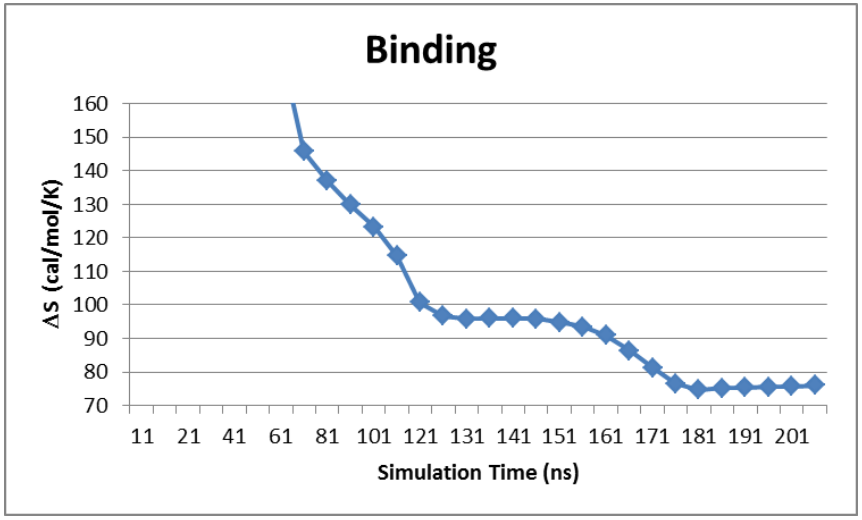
- PSD95 PDZ domain: 120 AA, 1821 atoms

# Quasi-Harmonic Analysis: PSD95-PDZ

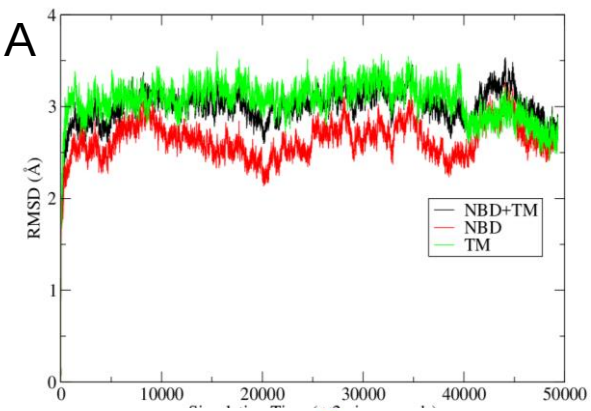


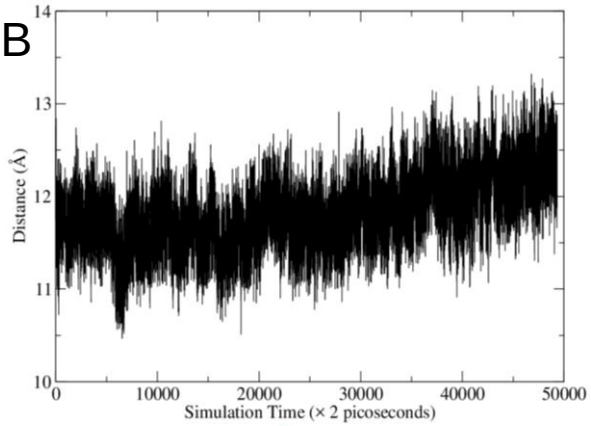



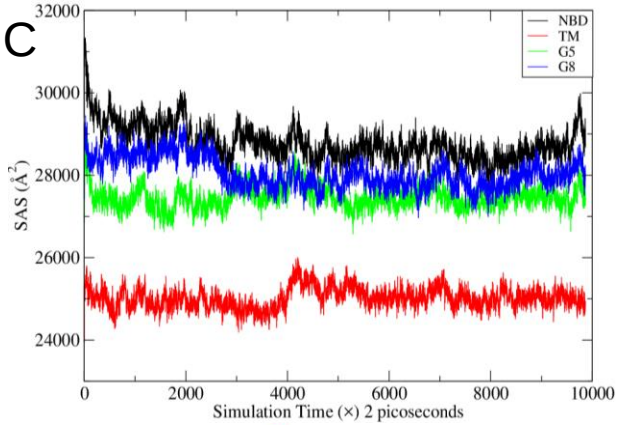



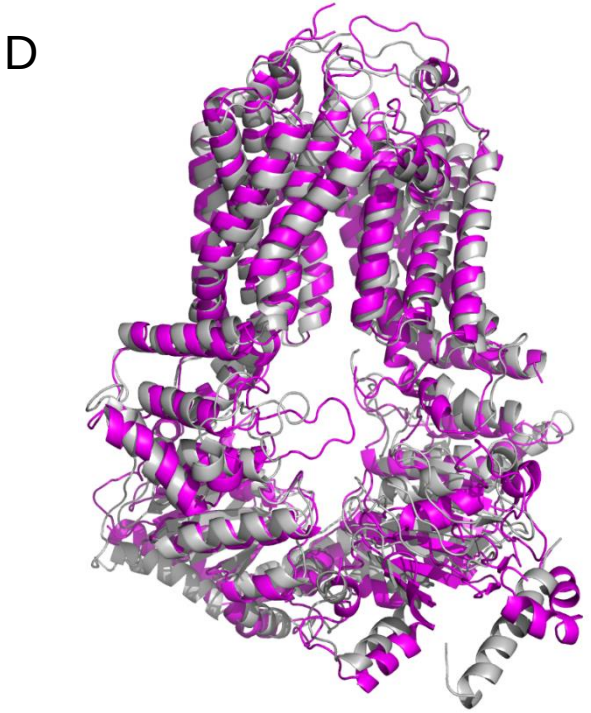



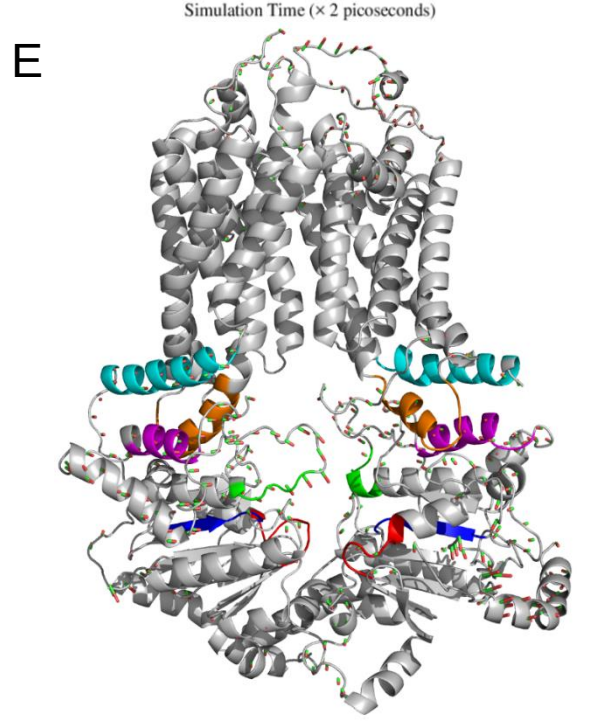
# Quasi-Harmonic Analysis: G5G8

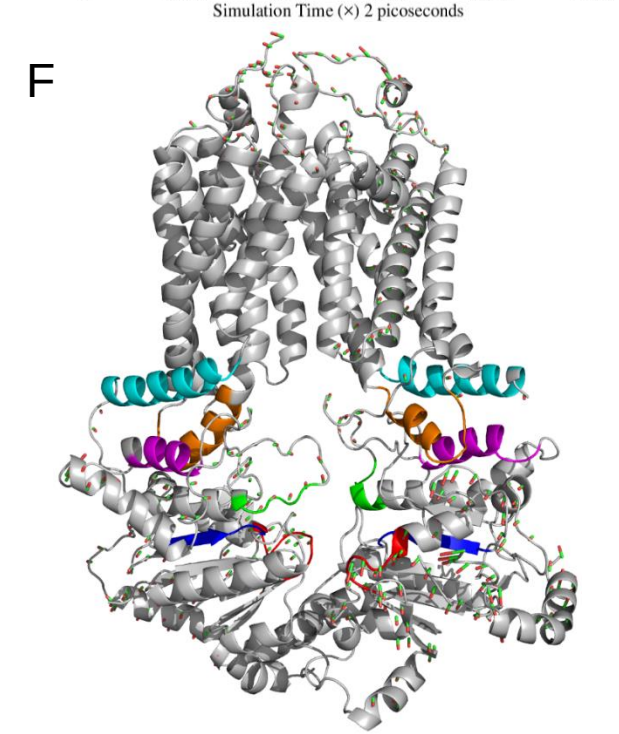


# Applications of Frequency Analysis

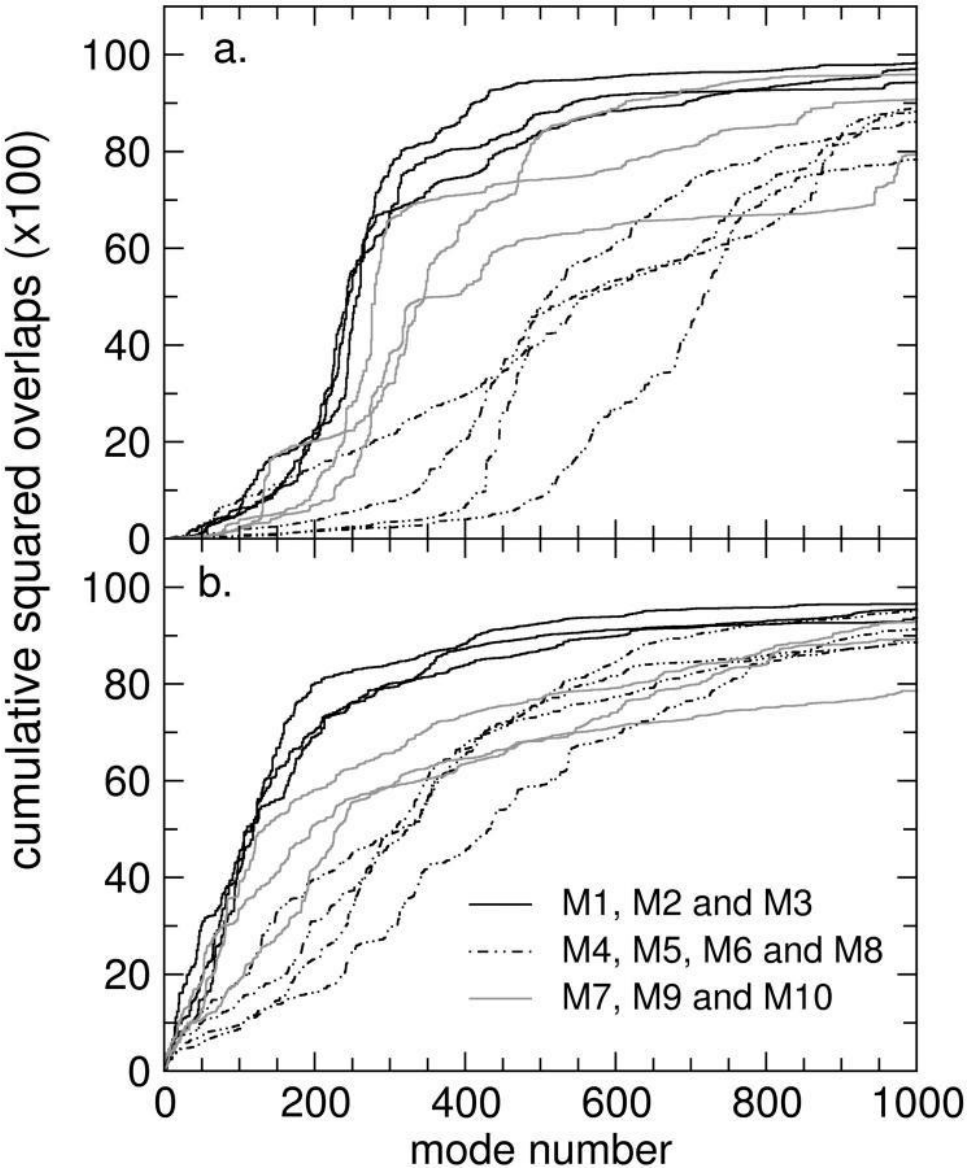
- Use all modes or a large subset
  - Analytical representation of a potential well
  - Limitations:
    - approximate nature of the harmonic approximation
    - Choice of a subset
- Properties of individual modes
  - Must avoid over-interpretation of the data
    - E.g., discussing differences of modes equal in energy
    - No more meaningful than discussing differences between motion in an arbitrarily chosen Cartesian coordinate system

# Applications of Frequency Analysis

- Explaining which modes/frequencies are involved in a particular domain's motion
- Answered using projection methods:
  - Normal modes form a basis of the configuration space of the protein
  - Given displacement d, $p_i = d \cdot e_i$
    - Contribution of mode i to the motion under consideration
  - Cumulative contribution of modes to displacement

$$C_k = \sum_{i=6}^{k} p_i^2, k = 1..3N$$

# Cumulative projections of transmembrane helices in Ca-ATPase




Cumulative summation of the squared overlap between the normal modes and the normalized rotation (*a*) and translation (*b*) vectors defined on the *Ca* atoms of each helix of the E1$Ca_2$ form (1eul). The cumulative squared overlaps (×100) are plotted against mode numbers (*x* axis restricted to modes 7–1000). .

*Reuter et al., Biophysical J., 85, 2186-2197, 2003*

# Summary on Frequency Analysis

1. Study a protein's function
   - Normal mode analysis (NMA)
   - Gaussian network model (GNM)
     I. Predicts experimental quantities related to flexibility, such as B-factors
     II. Site-site correlation
   - Essential dynamics
   - Quasi-harmonic analysis

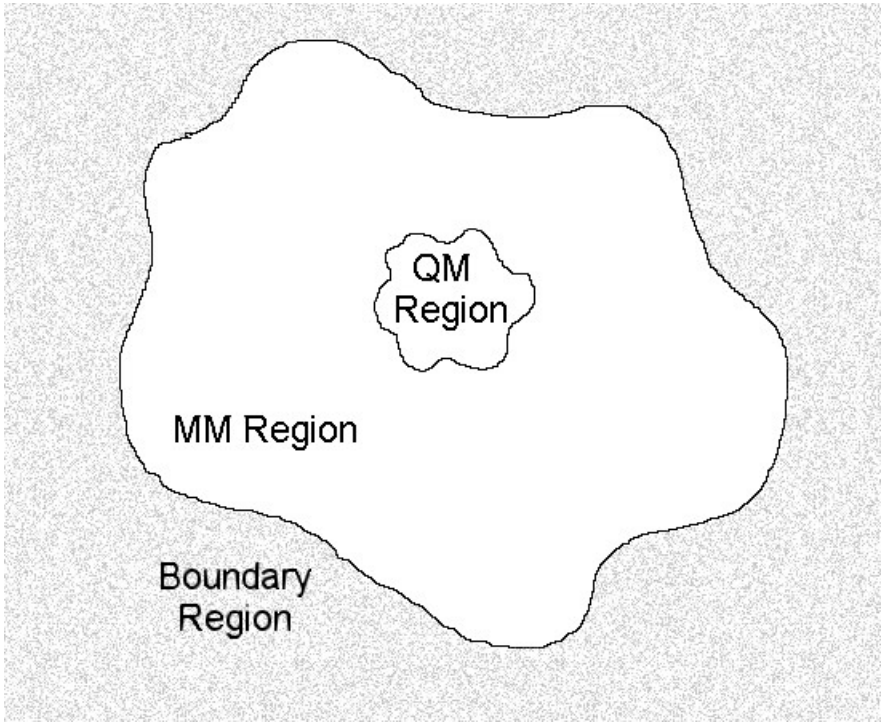
2. Calculate thermodynamic properties
   - Normal mode analysis
   - Quasi-harmonic dynamics

3. Thermodynamic properties
   - no sampling problem for NMA and GNM
   - Need extensive MD/MC sampling for essential dynamics and quasi-harmonic analysis

# Modeling Reaction

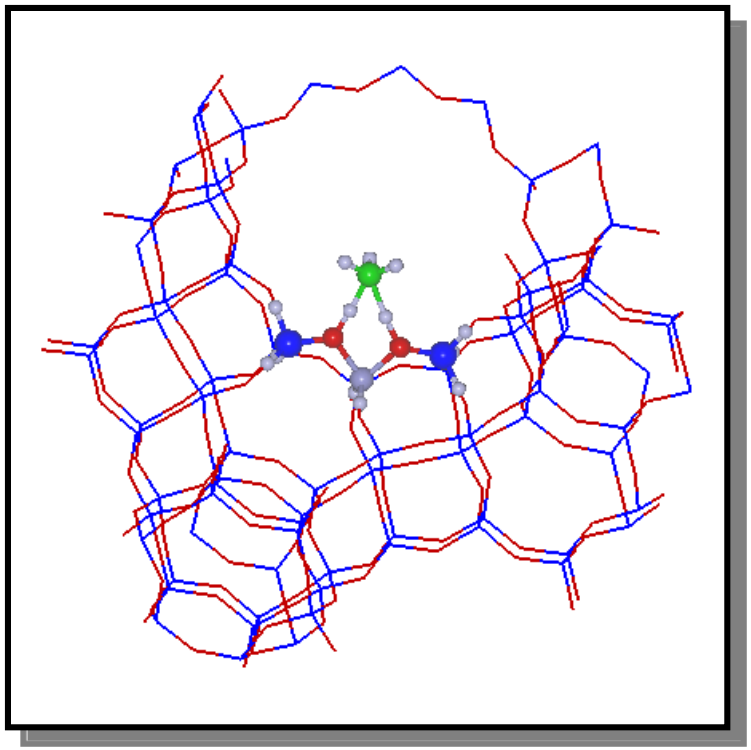
# A Hybrid QM/MM Approach

The development of hybrid QM/MM approaches is guided by the general idea that large chemical systems may be partitioned into an electronically important region which requires a quantum chemical treatment and a remainder which only acts in a perturbative fashion and thus admits a classical description.



# The QM/MM Modelling Approach

- Couple quantum mechanics and molecular mechanics approaches
- QM treatment of the active site
  - reacting centre
  - excited state processes (e.g. spectroscopy)
  - problem structures (e.g. complex transition metal centre)
- Classical MM treatment of environment
  - enzyme structure
  - zeolite framework
  - explicit solvent molecules
  - bulky organometallic ligands



# QM/MM Methods

- Construct a Hamiltonian for the system consisting of a QM region and an MM region

$$H = H_{QM} + H_{MM} + H_{QM/MM}$$

- QM and MM regions interact mechanically and electronically (electrostatics, polarization)

- If bonds cross boundary between QM and MM region:
  - Cap bonds of QM region with link atoms
  - Use frozen or hybrid orbitals to terminate QM bonds

# The Simplest Hybrid QM/MM Model

Hamiltonian for the molecular system in the Born-Oppenheimer approximation:

$$H = -\frac{1}{2}\sum_{i}^{electrons}\nabla^2 - \sum_{i}^{electrons}\sum_{j}^{nuclei}\frac{Z_j}{R_{ij}} + \sum_{i}^{electrons}\sum_{j<i}^{electrons}\frac{1}{r_{ij}} + \sum_{i}^{nuclei}\sum_{j<i}^{nuclei}\frac{Z_i Z_j}{R_{ij}}$$

←"Standard" QM Hamiltonian

$$H = -\frac{1}{2}\sum_{i}^{electrons}\nabla^2 - \sum_{i}^{electrons}\sum_{j}^{nuclei}\frac{Z_j}{R_{ij}} + \sum_{i}^{electrons}\sum_{j<i}^{electrons}\frac{1}{r_{ij}} + \sum_{i}^{nuclei}\sum_{j<i}^{nuclei}\frac{Z_i Z_j}{R_{ij}} \underbrace{- \sum_{i}^{electrons\,charges}\sum_{k}\frac{Q_k}{R_{ik}} + \sum_{i}^{nuclei\,charges}\sum_{k}\frac{Z_i Q_k}{R_{ik}}}_{Effect\ of\ External\ Charges}$$

The main drawbacks of this simple QM/MM model are:

- it is impossible to optimize the position of the QM part relative to the external charges because QM nuclei will collapse on the negatively charged external charges.
- some MM atoms possess no charge and so would be invisible to the QM atoms
- the van der Waals terms on the MM atoms often provide the only difference in the interactions of one atom type versus another, i.e. chloride and bromide ions both have unit negative charge and only differ in their van der Waals terms.

# A Hybrid QM/MM Model

So, it is quite reasonable to attribute the van der Waals parameters (as it is in the MM method) to every QM atom and the Hamiltonian describing the interaction between the QM and MM atoms can have a form:

$$\hat{H}_{QM/MM} = -\sum_{i}^{electrons}\sum_{j}^{MM\ atoms}\frac{Q_j}{r_{ij}} + \sum_{i}^{nuclei}\sum_{j}^{MM\ atoms}\frac{Z_i Q_j}{R_{ij}} + \sum_{i}^{nuclei}\sum_{j}^{MM\ atoms}\left\{\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}}\right\}$$

The van der Waals term models also electronic repulsion and dispersion interactions, which do not exist between QM and MM atoms because MM atoms possess no explicit electrons.

**A. Warshel, M. Levitt** // Theoretical Studies of Enzymic Reactions: Dielectric, Electrostatic and steric stabilization of the carbonium ion in the reaction of lysozyme. // ***J.Mol.Biol. 103(1976), 227-49***

# The Hybrid QM/MM Model

Now we can construct a "real" hybrid QM/MM Hamiltonian:

$$\hat{H} = \hat{H}_{QM} + \hat{H}_{QM/MM} + \hat{H}_{MM}$$

$$\hat{H}_{QM/MM} = -\sum_{i}^{electrons}\sum_{j}^{MM\ atoms}\frac{Q_j}{r_{ij}} + \sum_{i}^{nuclei}\sum_{j}^{MM\ atoms}\frac{Z_i Q_j}{R_{ij}} + \sum_{i}^{nuclei}\sum_{j}^{MM\ atoms}\left\{\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}}\right\}$$

$$\hat{H}_{QM} = -\frac{1}{2}\sum_{i}^{electrons}\nabla^2 - \sum_{i}^{electrons}\sum_{j}^{nuclei}\frac{Z_j}{R_{ij}} + \sum_{i}^{electrons}\sum_{j<i}^{electrons}\frac{1}{r_{ij}} + \sum_{i}^{nuclei}\sum_{j<i}^{nuclei}\frac{Z_i Z_j}{R_{ij}}$$

$$\hat{H}_{MM} = \sum_{bonds} K_b (R - R_0)^2 + \sum_{angles} K_\theta (\theta - \theta_0) + \sum_{dihedrals}\frac{V_\varphi}{2}(1 + \cos(n\varphi)) + \sum_{nonbonded}\left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{R_{ij}}\right]$$

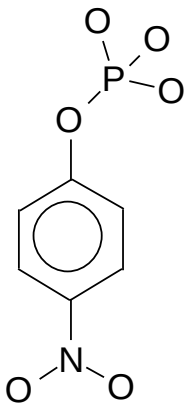
A "standard" MM force field can be used to determine the MM energy. For example, AMBER-like force field has a form:

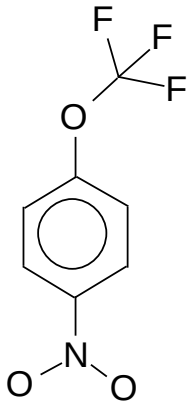
# Choice of QM method

... is a compromise between computational efficiency and practicality and the desired chemical accuracy.

The main advantage of semi-empirical QM methods is that their computational efficiency is orders of magnitude greater than either the density functional or ab initio methods

Calculation times (in time units)




| | | |
|---|---|---|
| 1800 | RHF/6-31G* | 36228 |
| 1 | PM3 | 1 |

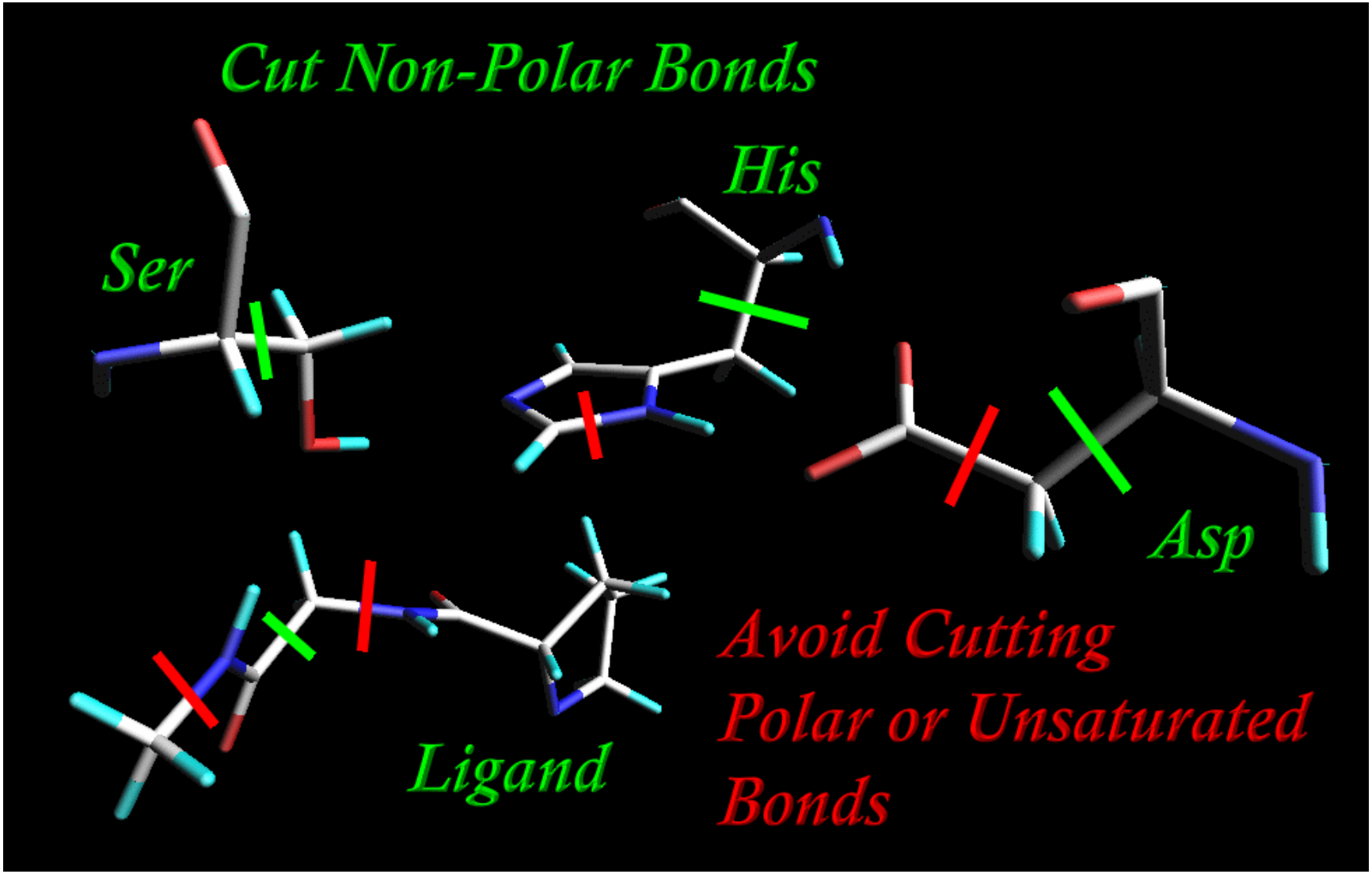
# Hints for running QM/MM calculations

## Choosing the QM region

- There are no good universal rules here
- One might want to have as large a QM region as possible
- However, having more than 80-100 atoms in the QM region will lead to simulations that are very expensive.
- for many features of conformational analysis, a good MM force field may be better than a semi-empirical or DFTB quantum description.

# Hints for running QM/MM calculations

## Choosing the QM region



# Hints for running QM/MM calculations
## Parallel Simulations

- At present all parts of the QM simulation are parallel except the density matrix build and the matrix diagonalisation.
- For small QM systems these two operations do not take a large percentage of time and so acceptable scaling can be seen to around 8 cpus.
- However, for large QM systems the matrix diagonalization time will dominate and so the scaling will not be as good.

# Amber QM/MM

- Amber features new and significantly improved QM/MM support
- The QM/MM facility supports gas phase, implicit solvent (GB) and periodic boundary (PME) simulations
- Compared to earlier versions, the QM/MM implementation offers improved accuracy, energy conservation, and performance.

# Amber QM/MM Example

**Example QMMM MD Script for Sander 9**

```
Example QMMM MD Script for Sander 9
 &cntrl
  imin=0, nstlim=10000,          (perform MD for 10,000 steps)
  dt=0.002,                      (2 fs time step)
  ntt=1, tempi=0.1, temp0=300.0  (Berendsen temperature control)
  ntb=1,                         (Constant volume periodic boundaries)
  ntf=2, ntc=2,                  (Shake hydrogen atoms)
  cut=8.0,                       (8 angstrom classical non-bond cut off)
  ifqnt=1                        (Switch on QM/MM coupled potential)
 /
 &qmmm
  qmmask=':753'                  (Residue 753 should be treated using QM)
  qmcharge=-2,                   (Charge on QM region is -2)
  qmtheory=1,                    (Use the PM3 semi-empirical Hamiltonian)
  qmcut=8.0                      (Use 8 angstrom cut off for QM region)
 /
```

# Amber QM/MM Example

Sample output

# Toward Accurate Calculation in Condensed-Phase Chemical Reaction: Electrostatically Embedded Multiconfiguration Molecular Mechanics Based on the Combined Quantum Mechanical and Molecular Mechanical Method

By Masahiro Higashi and Donald G. Truhlar

Combined quantum mechanical and molecular mechanical (QM/MM) methods have provided powerful means for studying chemical reactions in the condensed phase such as solutions, enzymes, and solids. In these approaches, the reaction center is described quantum mechanically, while the surroundings are treated by using a molecular mechanics force field. However, the high computational cost of quantum mechanical (QM) calculations prevents one from carrying out QM/MM molecular dynamics simulations with reliable accuracy and adequate sampling.

# Toward Accurate Calculation in Condensed-Phase Chemical Reaction: Electrostatically Embedded Multiconfiguration Molecular Mechanics Based on the Combined Quantum Mechanical and Molecular Mechanical Method

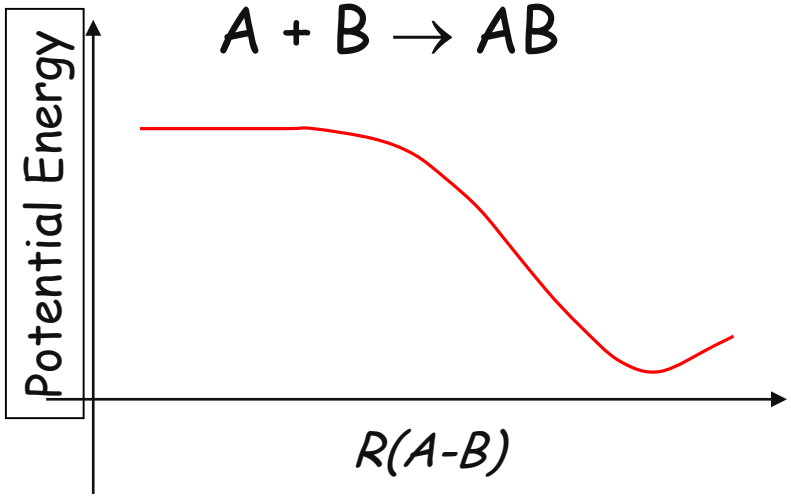
By Masahiro Higashi and Donald G. Truhlar

In order to reduce the computational cost of the QM calculation, we developed a new method called Electrostatically Embedded Multi-Configuration Molecular Mechanics (EE-MCMM) for generating global potential-energy surfaces (PESs) in the presence of an electrostatic potential. The global PESs of condensed-phase reactions can be determined by electronic structure calculations performed at some selected gas phase geometries. Due to the efficiency of this new method, high-level QM calculations can be applied to QM/MM methods.

The result is a key step toward studying chemical reactions in condensed phase with high-level QM calculations.

# Implementation and Application of Transition State Theory for Barrierless Association Reactions

The absence of a barrier in association reactions challenges theoretical chemists to understand the mechanism of reactions that occur in a wide variety of chemical environments, e.g., combustion chemistry, atmospheric chemistry, and interstellar chemistry.




- **Computer program development:**
  1. Implementing variable-reaction-coordinate transition state theory into the POLYRATE program to determine barrierless association reaction rates.
  2. Implementing master equations into the POLYRATE program to determine pressure-dependent rates and multi-well reactions.

- **Applications:**
  Mechanism of radical-radical and radical-molecule association reactions in combustion chemistry and atmospheric chemistry.

# $Cl^- + CH_3Cl' \rightarrow ClCH_3 + Cl'^-$

in aqueous solution

Equipotential contour plots of the PES calculated by the EE-MCMM method.

Equipotential contours plots of the difference between the PESs calculated by the EE-MCMM and direct methods.