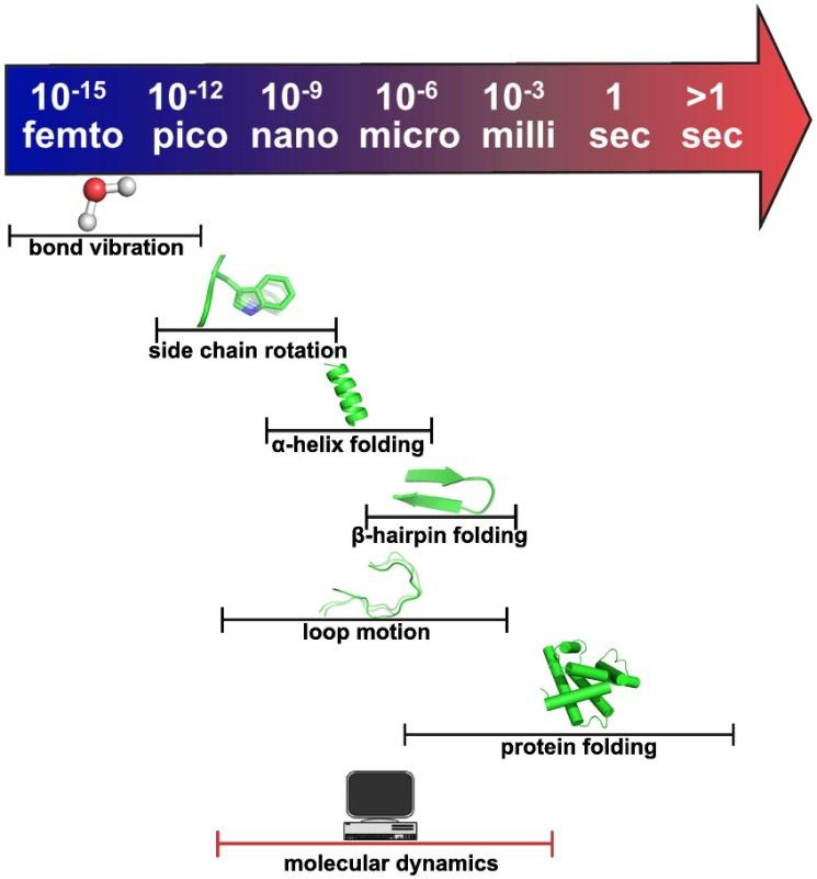
Normal Mode Analysis

Alexander Betz
16.7.2013

Time scale of protein motions



Source: Werner et al. 2012

Limitations of Molecular Dynamics:

- Only sampling of conformations close to initial conformation
- Resource consuming for large systems

What can we do ?

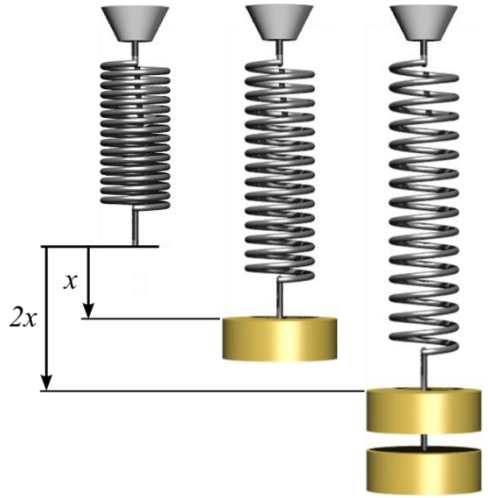
Harmonic Oscillator

Newton‘s second law of motion

$$F = ma = m\ddot{x}$$

Hooke‘s Law

$$F = -kx$$



Source: https://en.wikipedia.org/wiki/Hooke%27s_law

Harmonic Oscillator

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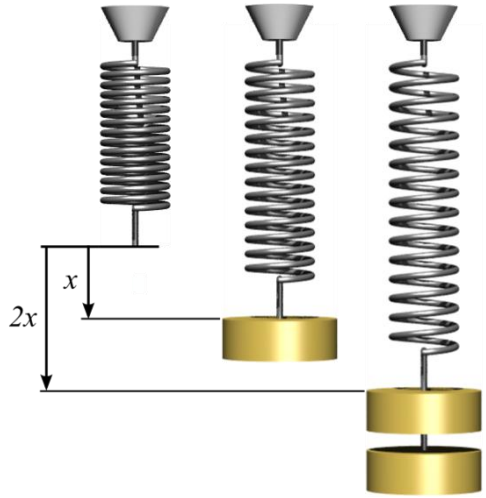
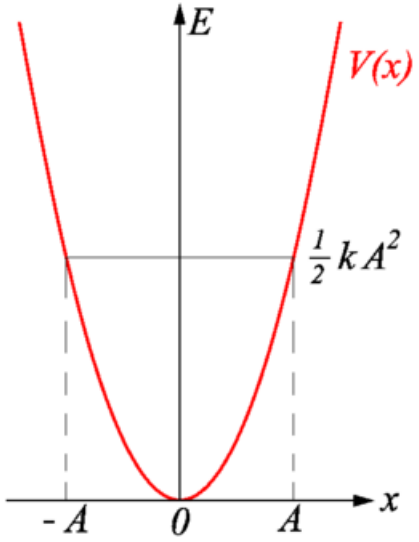


Source: https://en.wikipedia.org/wiki/Hooke%27s_law

Potential Energy Function

$$V(x) = \frac{1}{2}kx^2$$

$$F = ma = -\frac{dV}{dx} = -kx$$



Source: https://de.wikipedia.org/wiki/Harmonischer_Oszillator

Harmonic Oscillator

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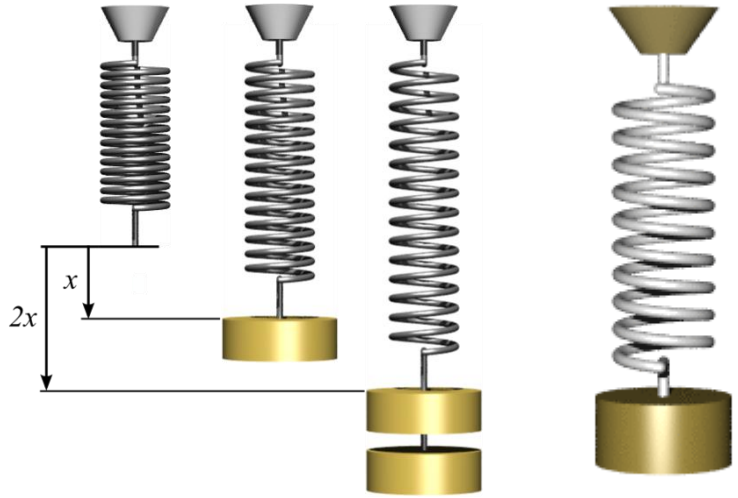

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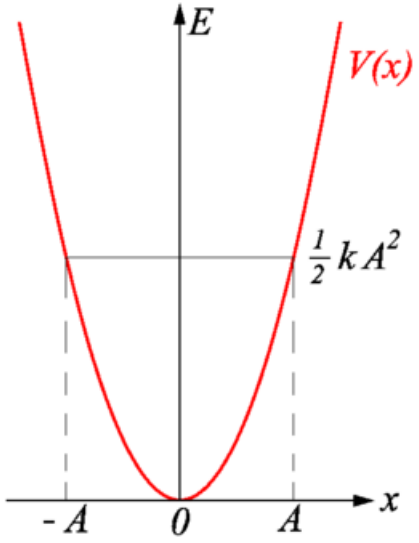
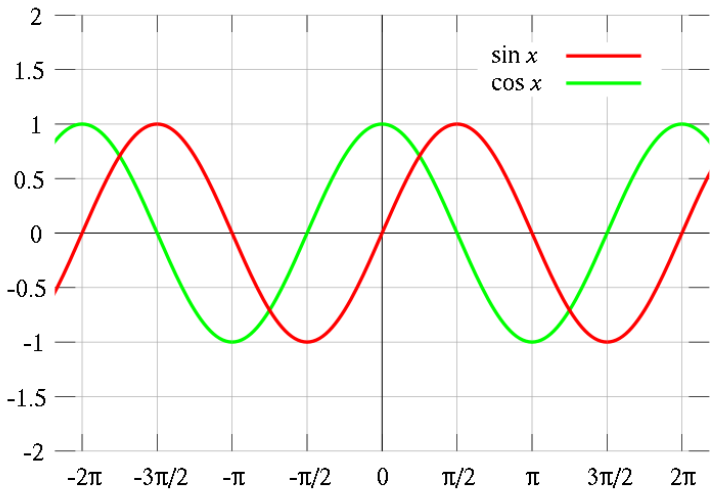


What is a normal mode ?

- Pattern of motion in an oscillating system in which all parts of the system move
  - sinusoidally
  - with the same frequency
  - with a fixed phase relation



Source: http://en.wikibooks.org/wiki/Trigonometry/Phase_and_Frequency

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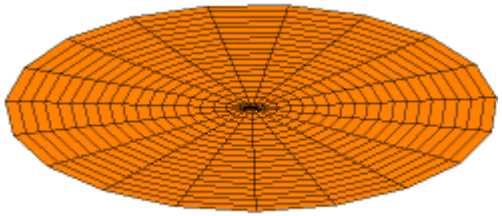
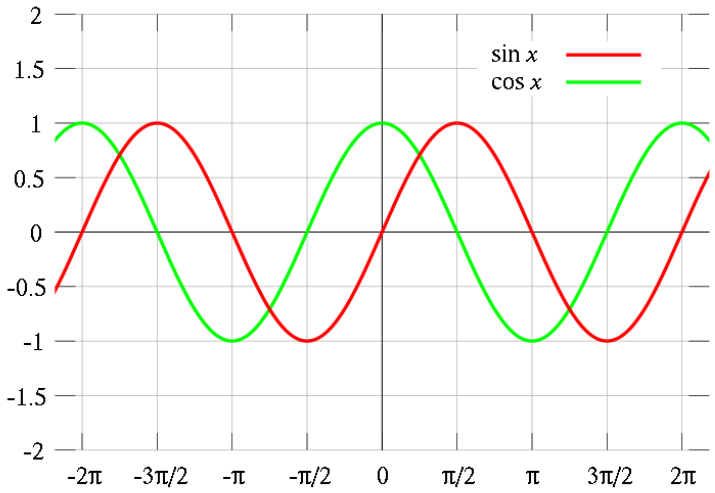




Source: http://en.wikipedia.org/wiki/Normal_mode

Source: http://en.wikibooks.org/wiki/Trigonometry/Phase_and_Frequency

General Algorithm

1. Determine a potential function for the system $V(x)$
2. Calculate matrix of force constants

$$\mathbf{H} = \begin{bmatrix} F_1 \\ F_2 \\ \vdots \end{bmatrix}$$

3. Diagonalize force constant Matrix

$$\mathbf{H} = \mathbf{A}^T \mathbf{M} \mathbf{A}$$

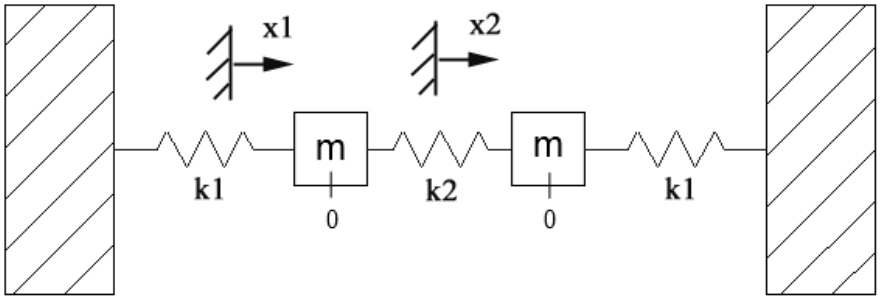
Eigenvector = normal mode

$$\mathbf{A} = (a_1 a_2 \cdots)$$

Eigenvalue = frequency

$$\mathbf{M} = \begin{bmatrix} \omega_1^2 & & 0 \\ & \omega_2^2 & \\ 0 & & \ddots \end{bmatrix}$$

Coupled Oscillator



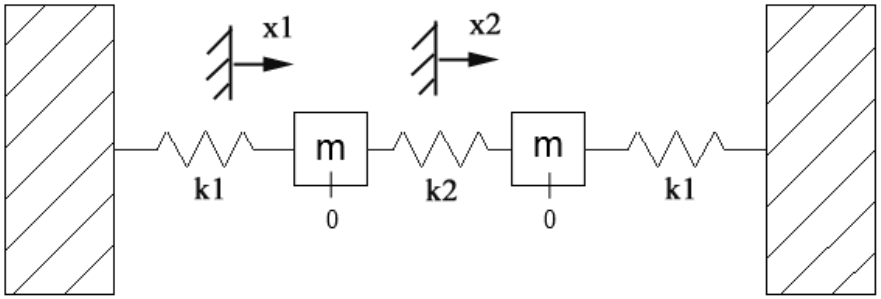
1. Get equations of motion

$$\vec{F}_1 = m\ddot{x} = -k_1 x_1 - k_2 x_1 + k_2 x_2$$

$$\vec{F}_2 = m\ddot{x} = -k_2 x_2 - k_1 x_2 + k_2 x_1$$

Source: http://lpsa.swarthmore.edu/MtrxVibe/Anims/VibrationAnimations.html

Coupled Oscillator



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2. Write in Matrix Form

$$\begin{bmatrix} -\frac{k_1 + k_2}{m} & \frac{k_2}{m} \\ \frac{k_2}{m} & -\frac{k_1 + k_2}{m} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} \ddot{x}_1 \\ \ddot{x}_2 \end{bmatrix}$$

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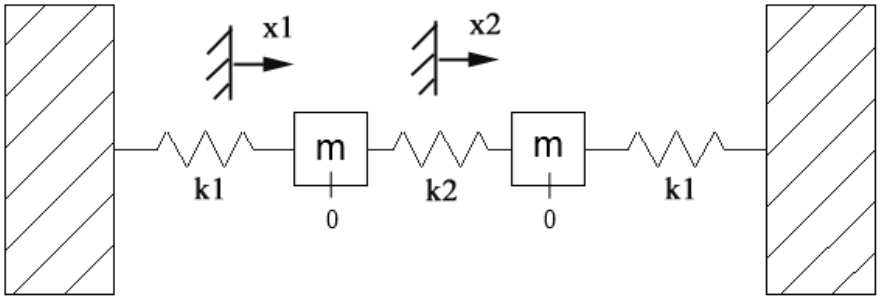

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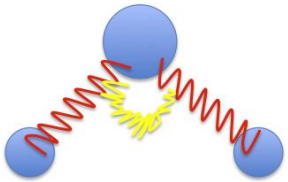
3. Get Eigenvalues and -vectors

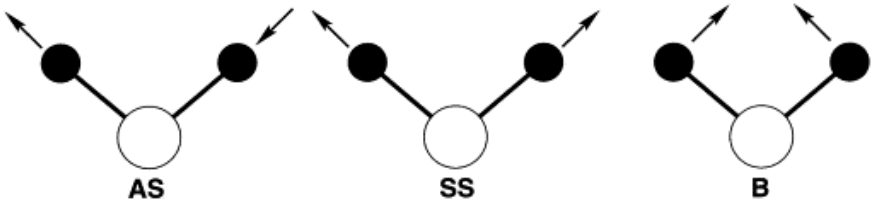
for $k_1 = k_2 = m = 1$

$$\mathbf{M} = \begin{bmatrix} 3 & 0 \\ 0 & 1 \end{bmatrix} \qquad \mathbf{A} = \begin{bmatrix} 1 & 1 \\ -1 & 1 \end{bmatrix}$$

Source: http://lpsa.swarthmore.edu/MtrxVibe/Anims/VibrationAnimations.html

Normal modes of water





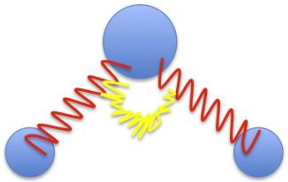
3N-6 normal modes

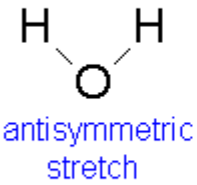
Application:
Microwaves with the freqency of one normal mode

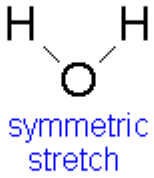
Spring model: Morrison et al 1999

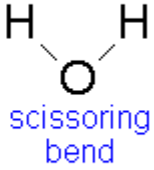
Normal modes of water: http://mini.physics.sunysb.edu/~marivi/TEACHING-OLD/PHY313/doku.php?id=lectures:5

Normal modes of water









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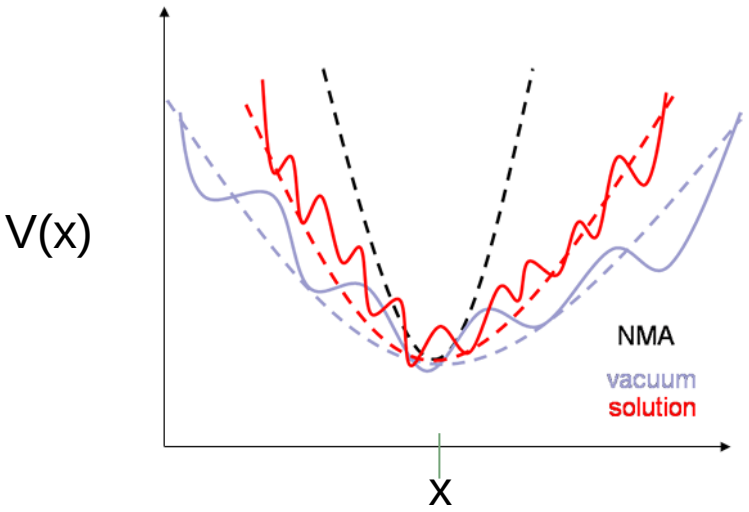
All-atom NMA

$$E_{total} = E_{Bond} + E_{Angle} + E_{Dihedral} + E_{VdW} + E_{Coulomb}$$

Harmonic approximation



http://mmb.irbbarcelona.org/FlexServ/help/introduction.php

All-atom NMA

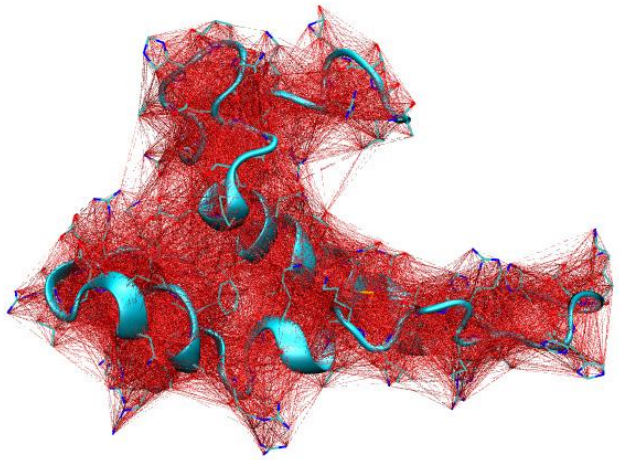
- Low frequency modes resemble slow motions
- Slow motions are the ones of interest, because these are the global motions

- NMA only captures harmonic motions
- Only the harmonic part of global motions can be captured
- Still gives a good indication of a proteins dynamics

Problems of all atom NMA

- Selection of force field is crucial
- Structure needs to be minimized
- Large 3n x 3n matrix to diagonalize
  - does not fit in current memory for large systems
  - Diagonalization is in $O(n^3)$

Elastic Network Models



Source: http://sbg.cib.csic.es/Software/iMOD/

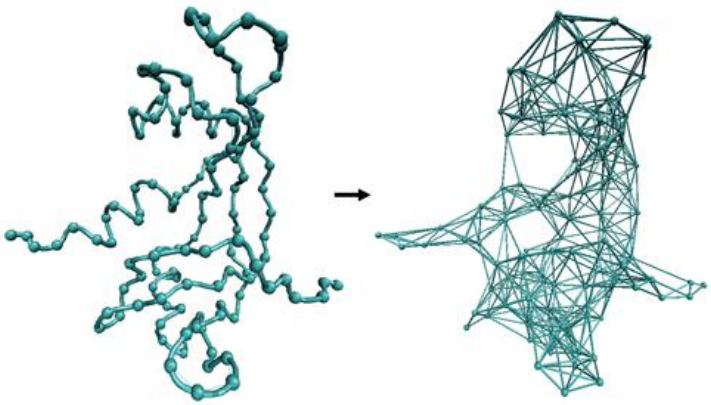
- First proposed by M. Tirion in 1996
- Consider all atoms
- Connect atoms within a predefined cutoff range with a spring
- System is already at equilibrium
- Simple Energy function

$$V = \frac{1}{2} k_e (d - d_e)$$

$$d = | \vec{r}_i - \vec{r}_j |$$

- Same constant for all springs

Gaussian Network Model



Source: http://mmb.pcb.ub.es/FlexServ/help/NMA.php

- Ivet Bahar et al.(1997)
- Consider only Cα
- Matrix size is reduced by a factor of ~60^2
- Results correlate with experiments
- Isotropic = no directional information

Anisotropic network model

- Atilgan,Bahar et al. (2001)
- Adds directionality to Gaussian model

- Hessian Matrix

$$\mathbf{H} = \begin{bmatrix} H_{11} & \cdots & H_{1n} \\ \vdots & \ddots & \vdots \\ H_{n1} & \cdots & H_{nn} \end{bmatrix}$$

$$H_{ii} = \begin{bmatrix} dxdx & dxdy & dxdz \\ dydx & dydy & dydz \\ dzdx & dzdy & dzdz \end{bmatrix}$$

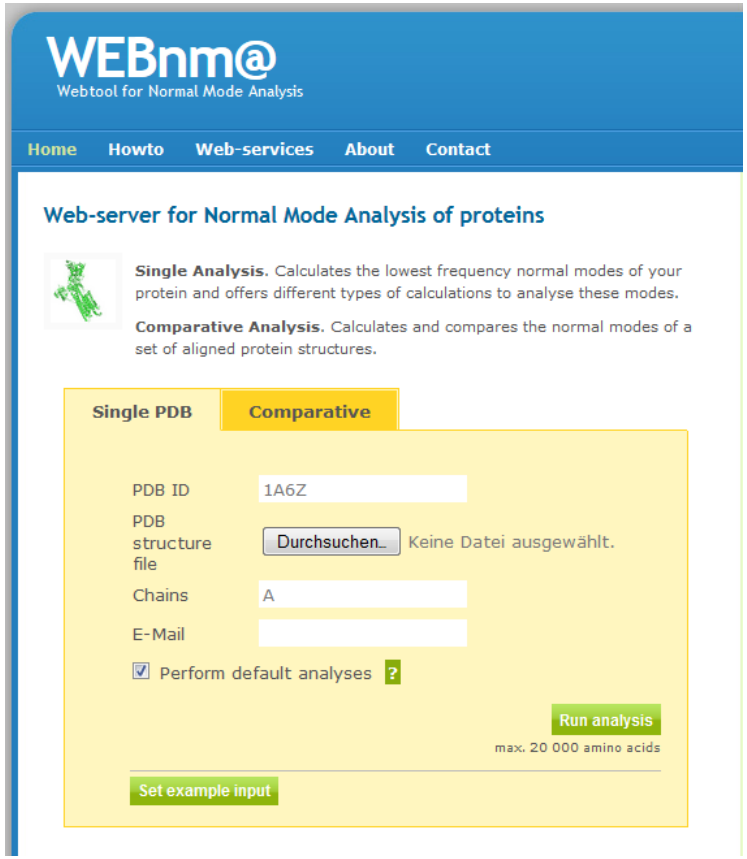
Applications

- Analyzation of
  - domain motions
  - protein complex movements
  - protein movements upon ligand binding
  - viral capsid movements
  - residue flexibility(B factors)

WebNMA

- Server for NMA with a Gaussian Network Model
  - Input
    - PDB-ID and chain
  - Output
    - Lowest frequency normal modes + visualization
    - Average residue displacements
    - Matrix of correlated residue motions

WebNMA-Example



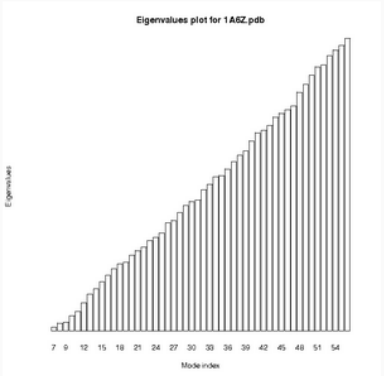
Deformation Energies

Below are the values of the deformation energy for the lowest-frequency non-trivial modes (modes 7 to 20).

Mode Index	Deformation Energy	Mode Index	Deformation Energy
7	325.91	14	4752.60
8	817.13	15	5868.42
9	849.13	16	6774.21
10	1452.95	17	8172.48
11	1876.97	18	7714.33
12	2972.27	19	8225.10
13	4459.34	20	9852.46

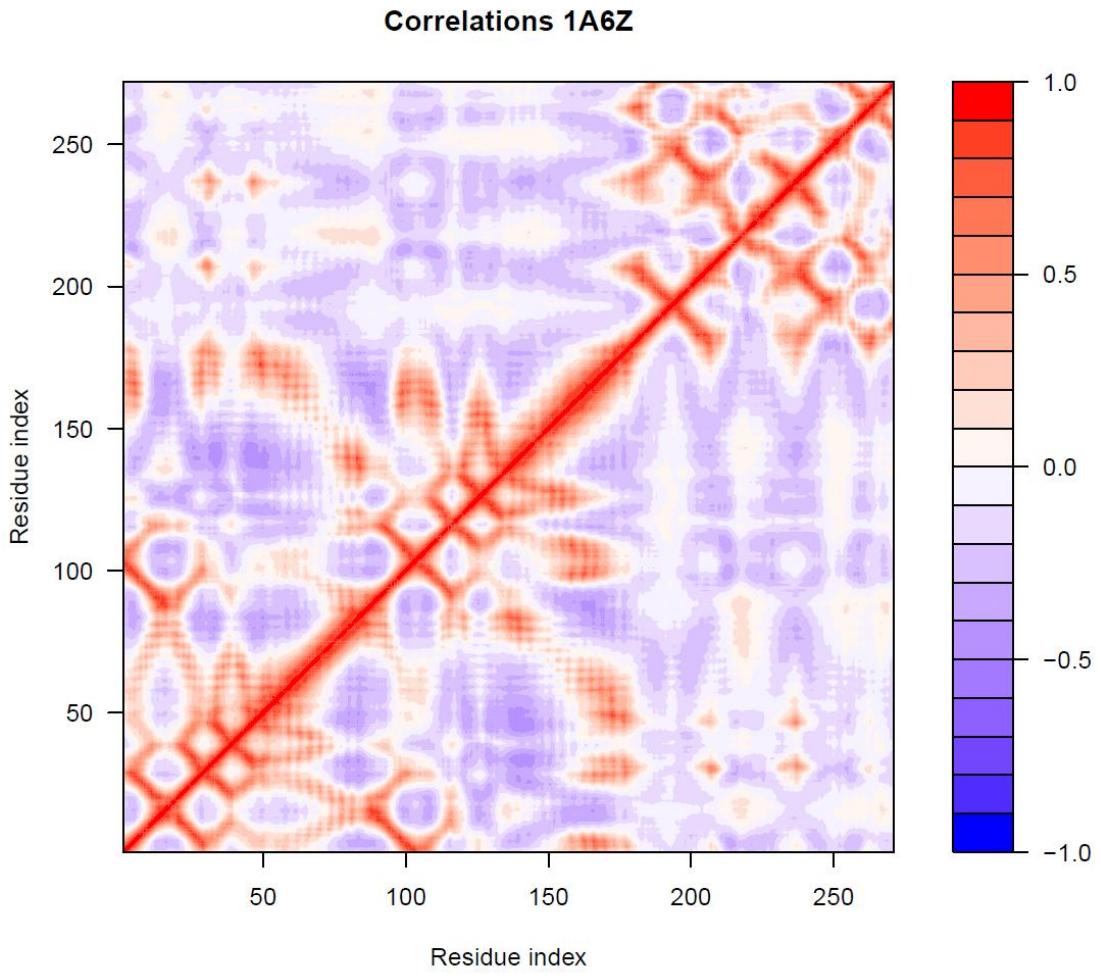
Eigenvalues

The eigenvalues for the lowest-frequency non-trivial modes.

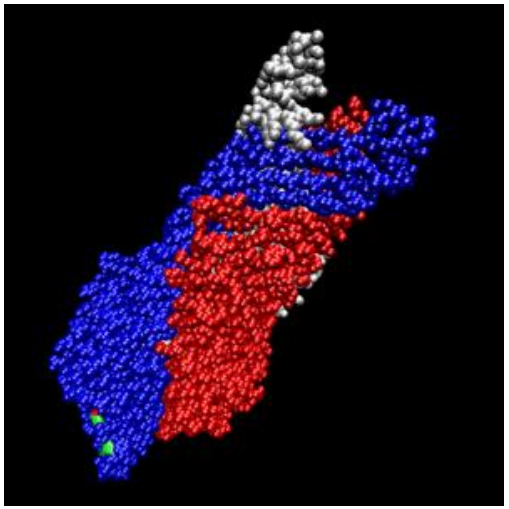


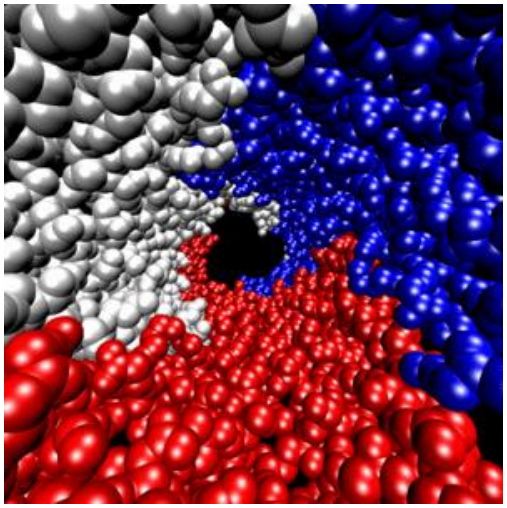
Higher resolution (pdf)

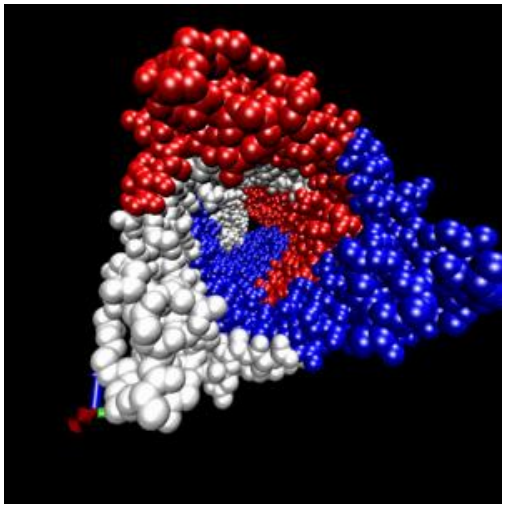
Correlated motions of residues



E. Coli Membrane Channel TolC







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

Conclusion

- NMA can be used to study the harmonic part of global protein motions based purely on the protein topology
- Can be used in conjuction with alternative conformations(e.g. from Cryo-EM) to determine protein motions

References

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- Wieniger et al.,ATP Binding Enables Broad Antibiotic Selectivity of Aminoglycoside Phosphotransferase(3′)-IIIa: An Elastic Network Analysis, *J. Mol.Biol.,* 2011
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- Hinsen, Analysis of Domain Motions by Approximate Normal Mode Calculations, PROTEINS, 1998
- *Tirion M.,* Large Amplitude Elastic Motions in Proteins from a Single-Parameter, Atomic Analysis, *Physical Review Letters*, 1996

Thank you for your attention!

If you have any questions, feel free to ask.

Bonus: Physical Interpretation

A linear transformation

$$f : V \rightarrow W$$

from Vector space V to vector space W, is defined by a matrix A.
The eigenvectors of A are those vectors of V that do not change their orientation when A is applied to them. They are only scaled by the eigenvalue of the corresponding eigenvector.
If we consider an eigenvector of A as one possible system configuration, then the transformation defined by A will keep the ratio between the elements of the system (=vector orientation) the same.
The eigenvectors therefore correspond to the normal modes.