The Essential Dynamics of Thermolysin: Conformation of Hinge-Bending Motion and Comparison of Simulations in Vacuum and Water

Van Aalten, D. M. F., Amadei, A., Vriend, G., Linssen, A. B. M., Venema, G., Berendsen, H. J. C. & Eijsink, V. G. H. (1995a). Proteins: Struct. Funct. Genet. 22, 45-54

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Introduction

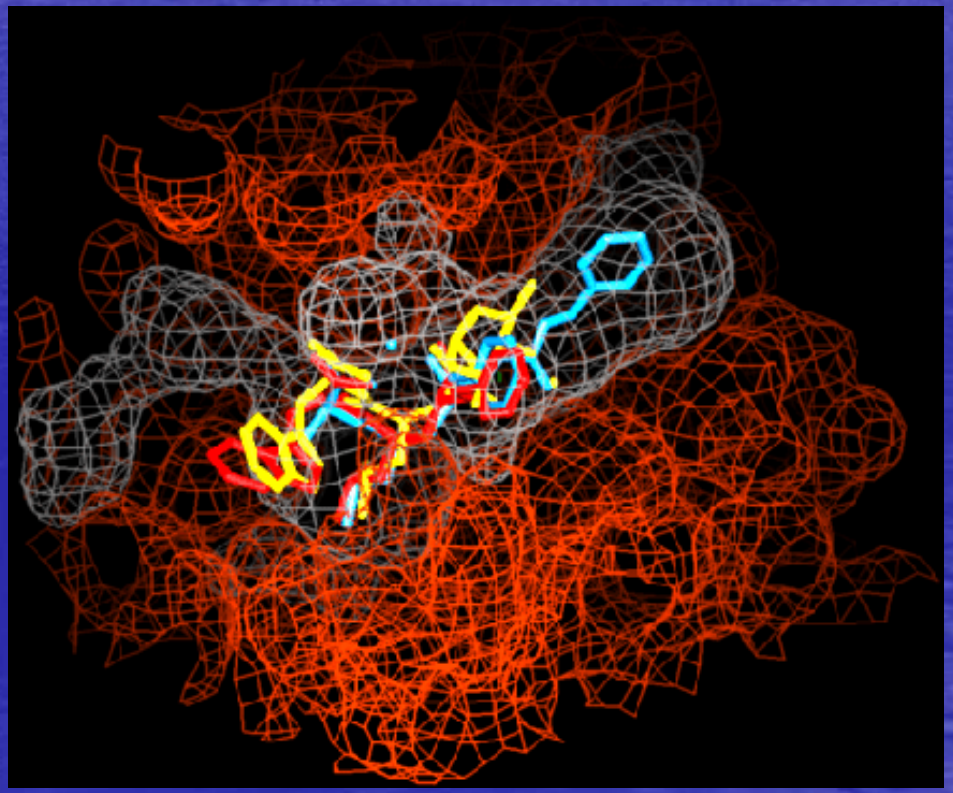
- Thermolysin
- Experimental Techniques:
  - X-ray crstallography, NMR, cryo-EM etc
- Comuter Simulations: Molecular Dynamics
  - Covariance Matrix
  - Eigen Value fluctuations
- Hinge Formation
- Results
- Recent Applications

Thermolysin (TLN)

- **Thermostable Extracellular Metalloendopeptidase (Neutral Proteases- NP)**
- **300-319 residues**
- **Structure:**

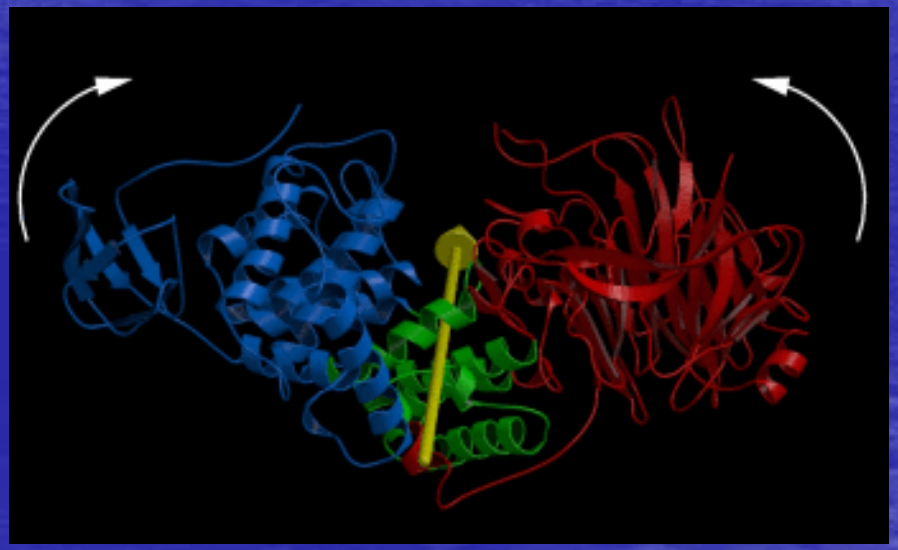
N – α–helix – C

- **Active site**
  - **Between N and C domains**
  - **Catalytically essential Zinc**

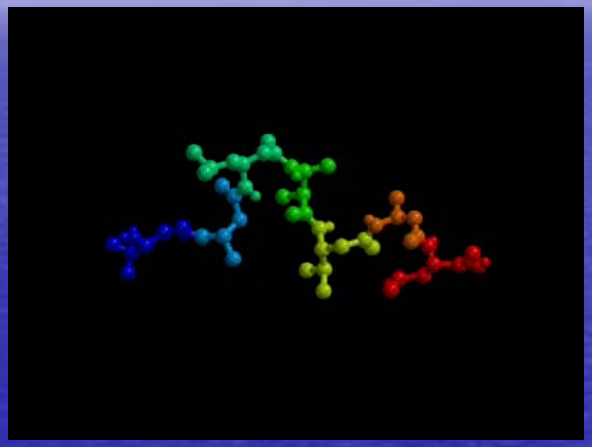


Hinge Formation

- TLN- Bacillus and NP-cerrus crystal structure comparison
- Opens and closes the NP active site
- Static comparisons
- Essential dynamics



Molecular Dynamics (MD)



- Theoretical studies of biological molecules permit the study of relationship between structure, function and dynamics on atomic level.
- MD calculates “real” dynamics of the system, from which time average properties can be calculated.

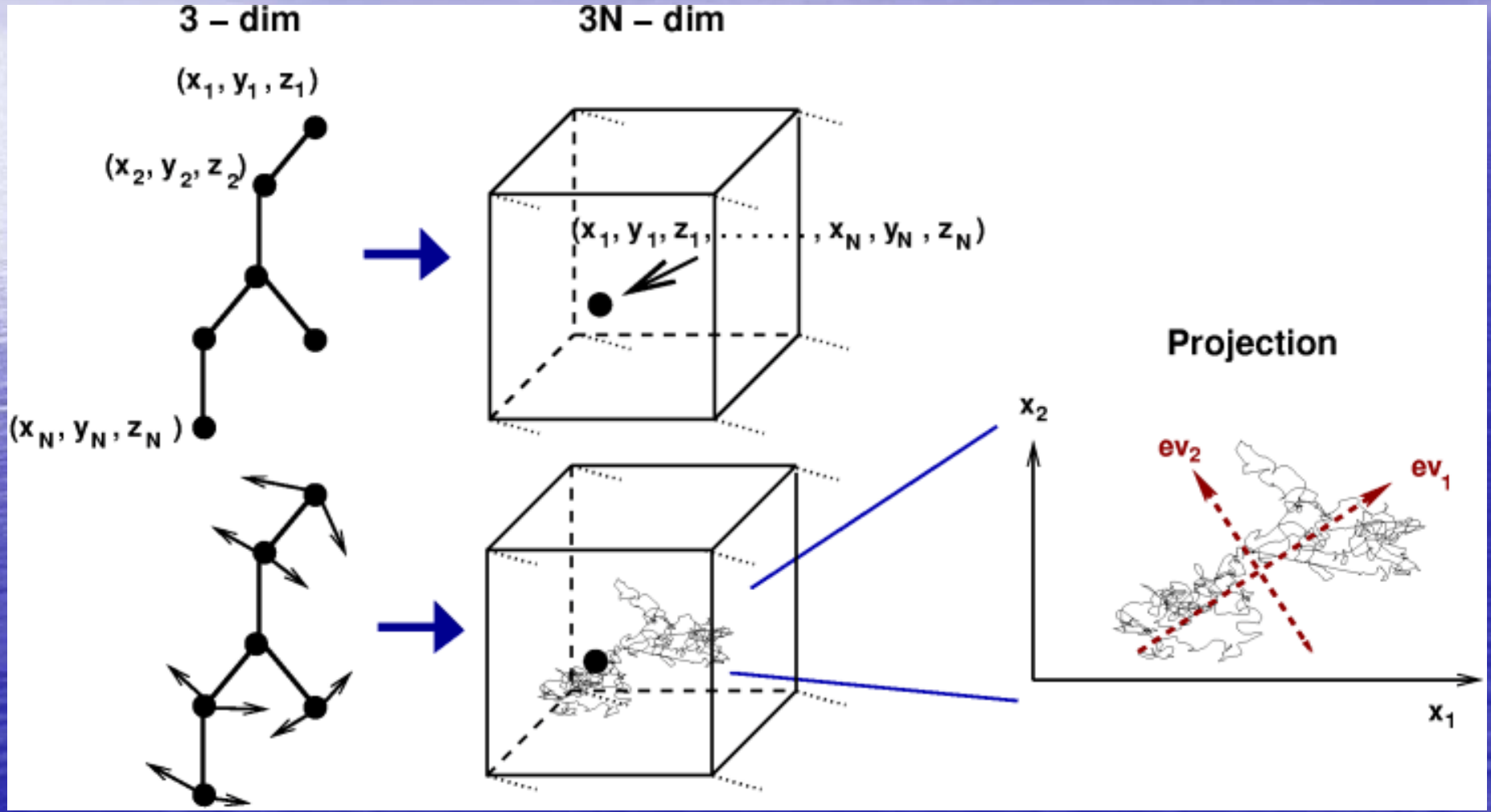
Inputs:

1) coordinate of atoms, pdb file from protein data bank.
2) potential energy function, determine atomic interaction forces.

MD cont'd...

- Force Fields:
  - Four component picture of the intra and inter molecular forces with in the system
  - Provides a function to describe energy change
  - As opposed to quantum mechanical methods,
    - Ignore the electronic motions
    - calculations are not time consuming
  - Transferability

MD cont'd ... matrix



MD cont'd ...

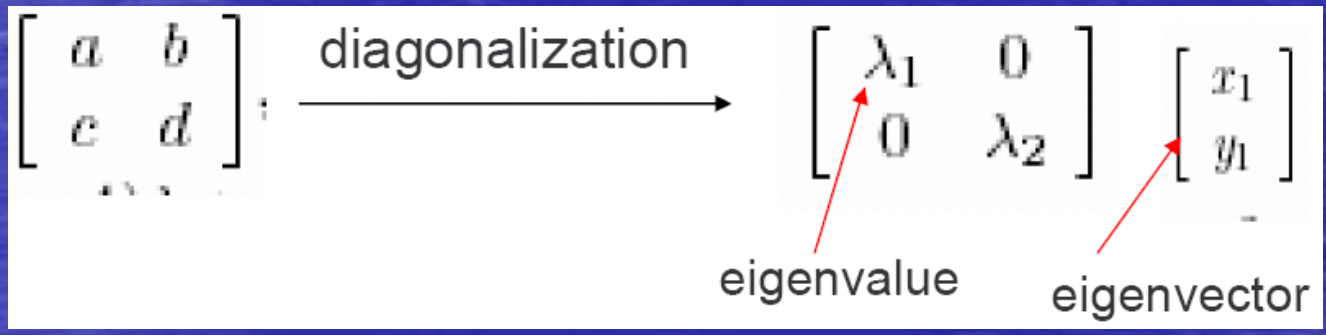
- Covariance Matrix

  $\langle x_i \rangle$ $x_i - \langle x_i \rangle$

  – Build covariance matrix of positional fluctuations.

  $$COV(x_i x_j) = \langle (x_i - \langle x_i \rangle)(x_j - \langle x_j \rangle) \rangle$$

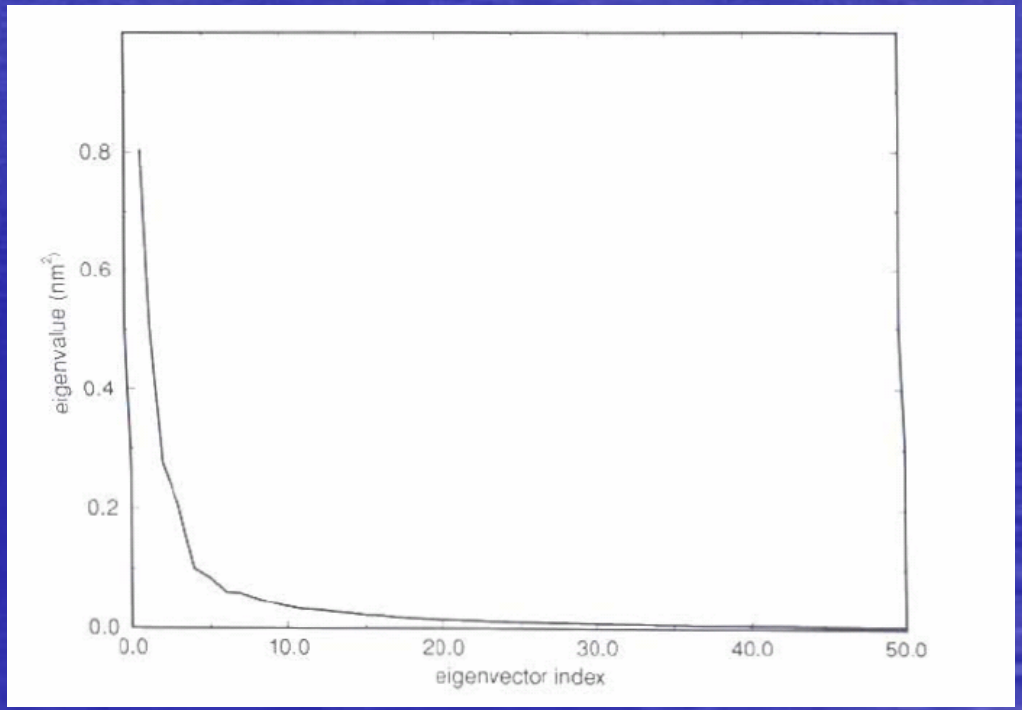
  – Diagonalize this matrix



  – Sort in descending order

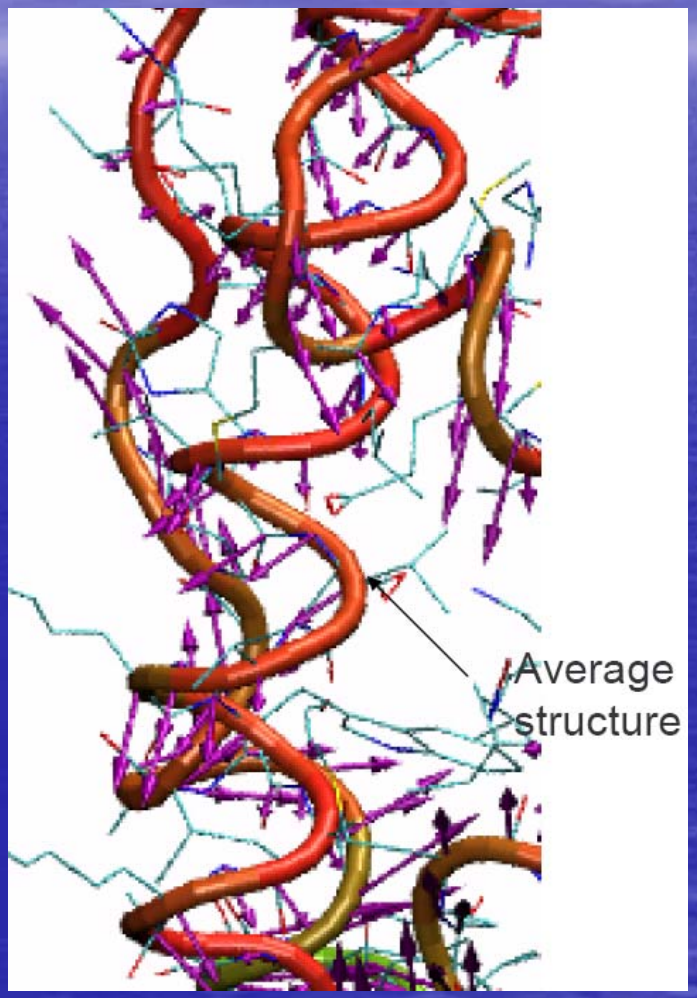
MD cont'd ...

- Proteins have only few large Eigen values and corresponding eigenvectors - essential subspace of motion
- All others – small high frequency and small amplitude motions can be neglected



MD cont'd ...

- Essential motions determine low energy modes of protein movement
- Atom components of these modes are presented by arrows that show the relative amplitude and direction of the displacement of the atoms from the averaged over MD trajectory structure



MD cont'd ...

Newton's laws F= Ma $\frac{d^2 r_i}{dt^2} = F_i(r_1, r_2, \cdots, r_n) \Big/ m_i$

$$F_i(r_1, r_2, \cdots, r_n) = -\nabla V(r_1, r_2, \cdots, r_n) \qquad i = 1, 2, \cdots, N$$

$$V_i(\vec{r}) = V_i(\vec{r}_1, \vec{r}_2, \vec{r}_3, \ldots, \vec{r}_N)$$

$$= \sum_{bonds} \frac{1}{2} K_b (b - b_0)^2 + \sum_{angles} \frac{1}{2} K_q (q - q_0)^2 + \sum_{improper} \frac{1}{2} K_x (x - x_0)^2 +$$

$$\sum_{dihedral} K_j \left[1 + \cos(n_j - d)\right] + \sum_{ij} \left[\frac{C_{12}}{r_{ij}^{12}} - \frac{C_6}{r_{ij}^6} - \frac{q_i q_j}{4\pi\varepsilon_0 \varepsilon_g r_{ij}} \right]$$

MD cont'd ...

Potential Energy

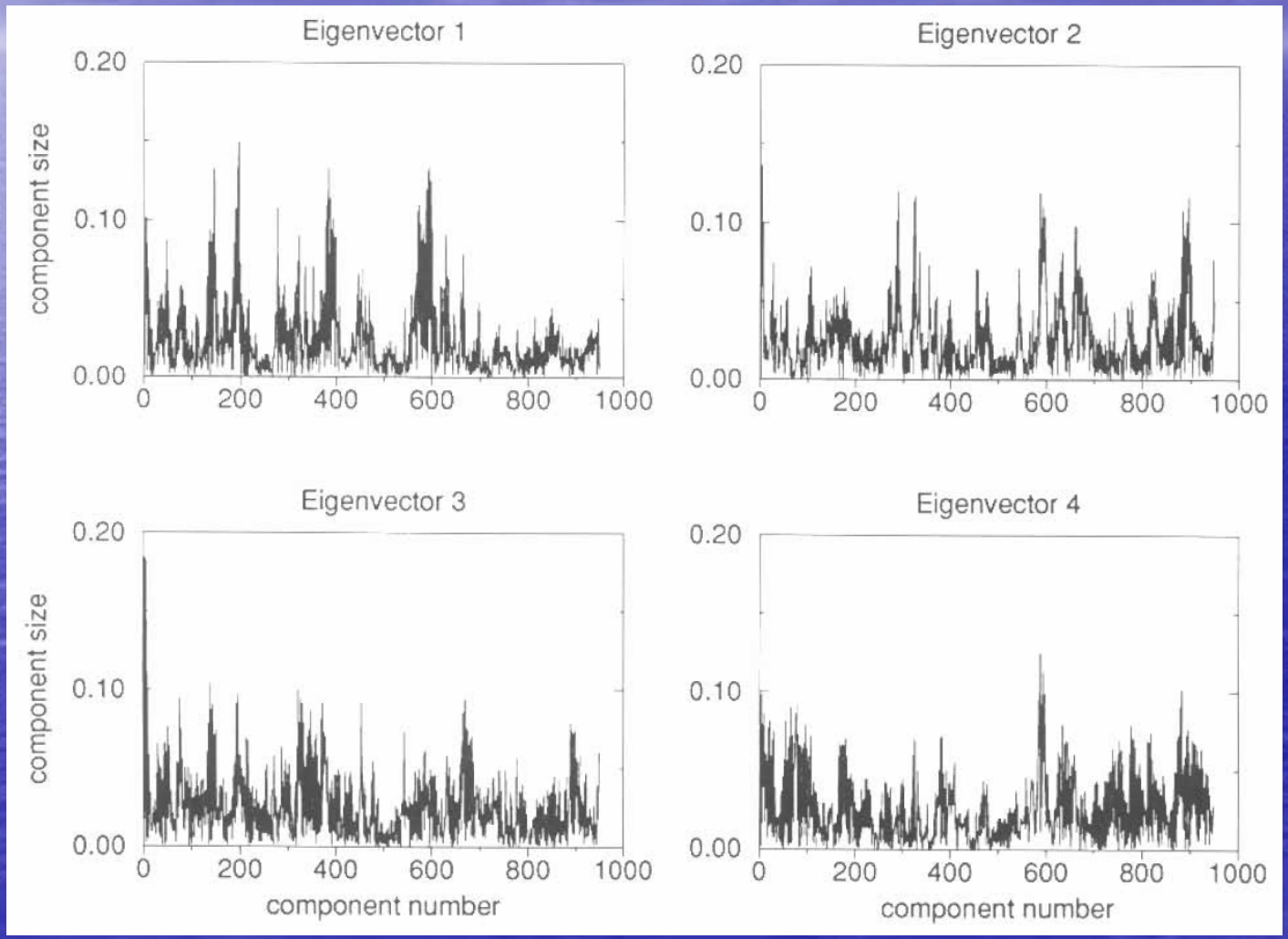
- Bonded forces (bonds angles, dihedrals, impropers)
- Non-bonded forces (coulomb, Van der Waals)

$$V_i(\vec{r}_1, \vec{r}_2, \vec{r}_3, \ldots, \vec{r}_N)$$

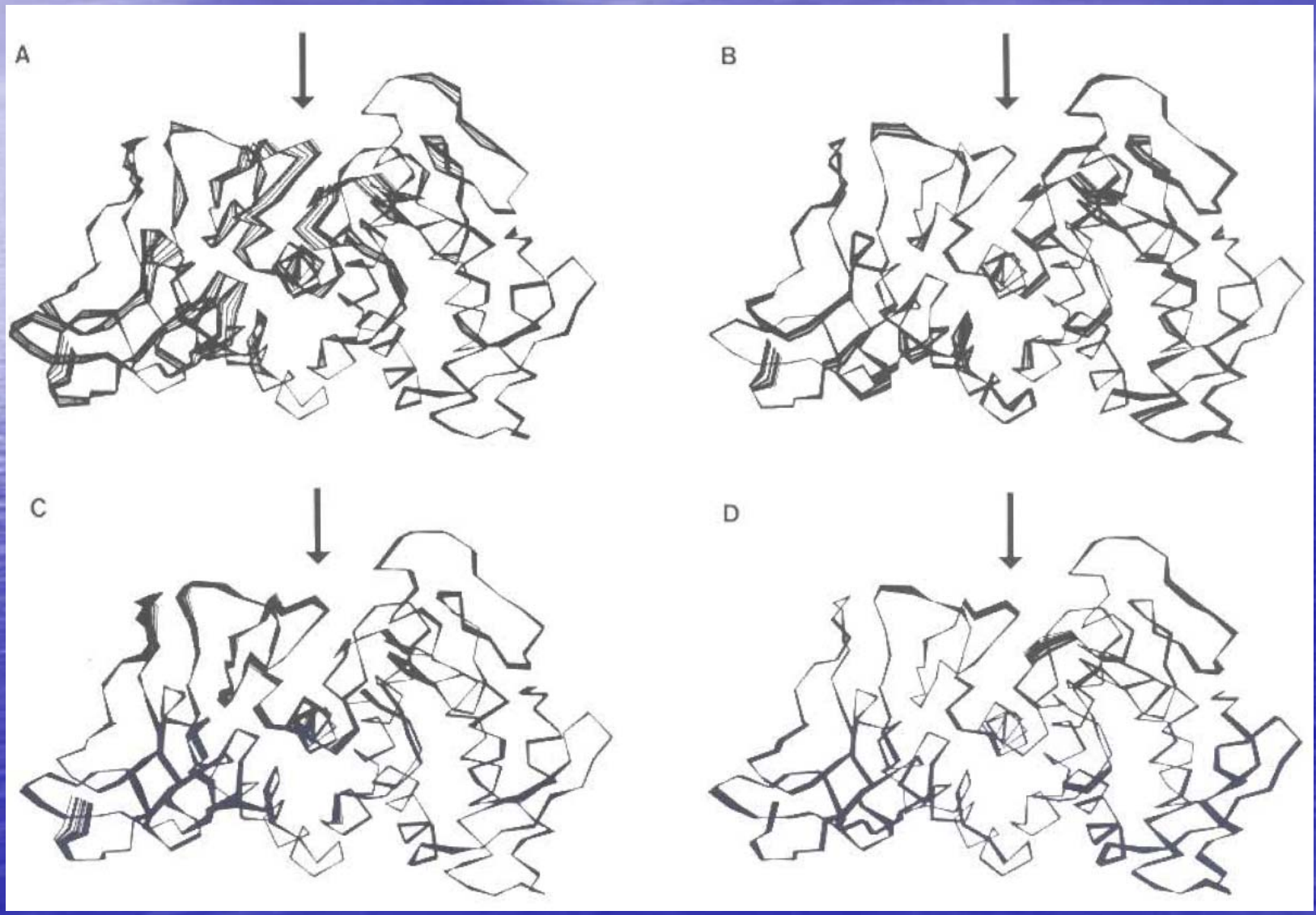
$$= \sum_{bonds} \frac{1}{2} K_b (b - b_0)^2 + \sum_{angles} \frac{1}{2} K_q (q - q_0)^2 + \sum_{improper} \frac{1}{2} K_x (x - x_0)^2 +$$

$$\sum_{dihedral} K_j \left[1 + \cos(n_j - d) \right] + \sum_{ij} \left[\frac{C_{12}}{r_{ij}^{12}} - \frac{C_6}{r_{ij}^6} - \frac{q_i q_j}{4\pi\varepsilon_0 \varepsilon_g r_{ij}} \right]$$

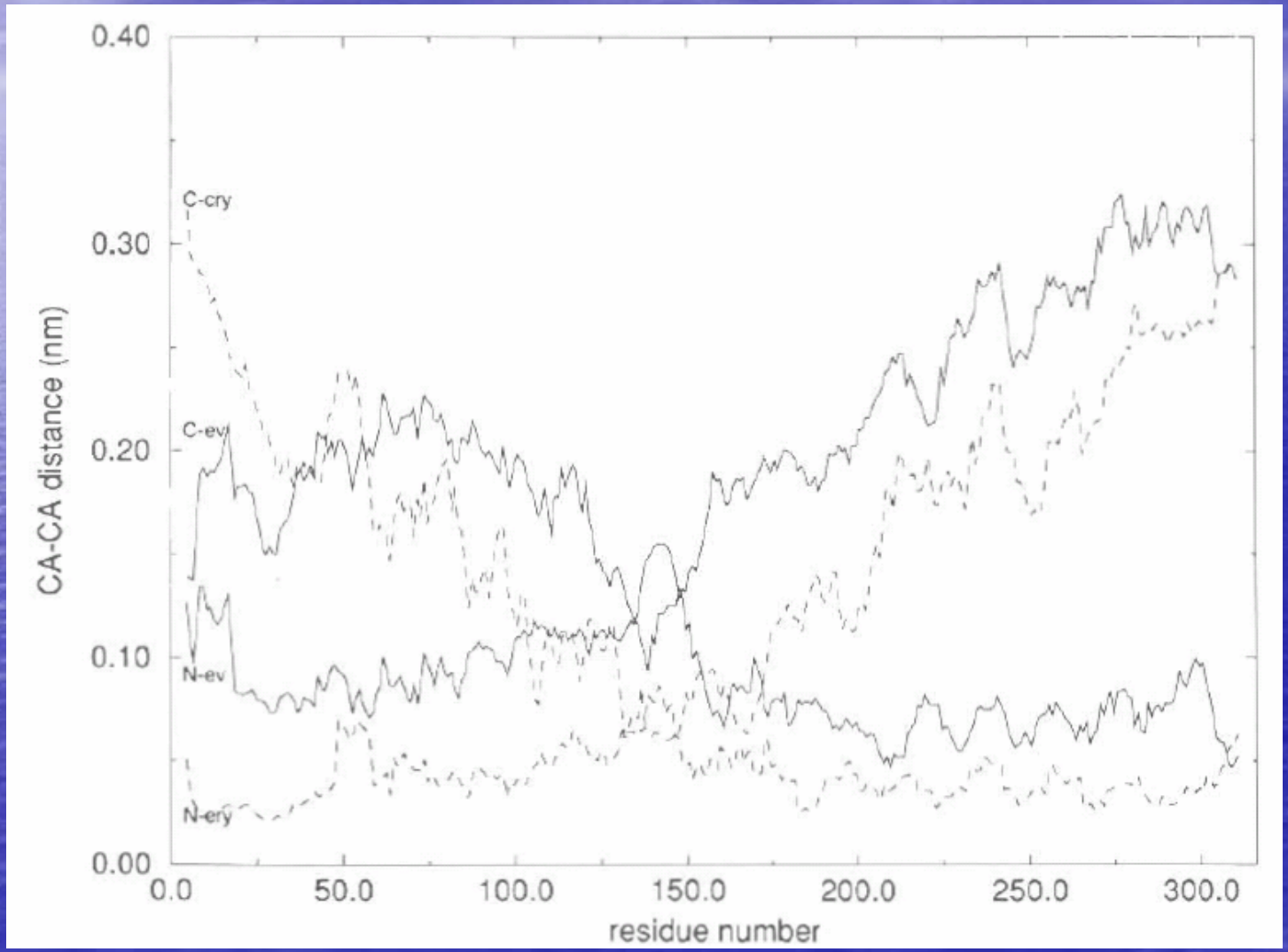
Results: Components of the First Four Eigenvectors



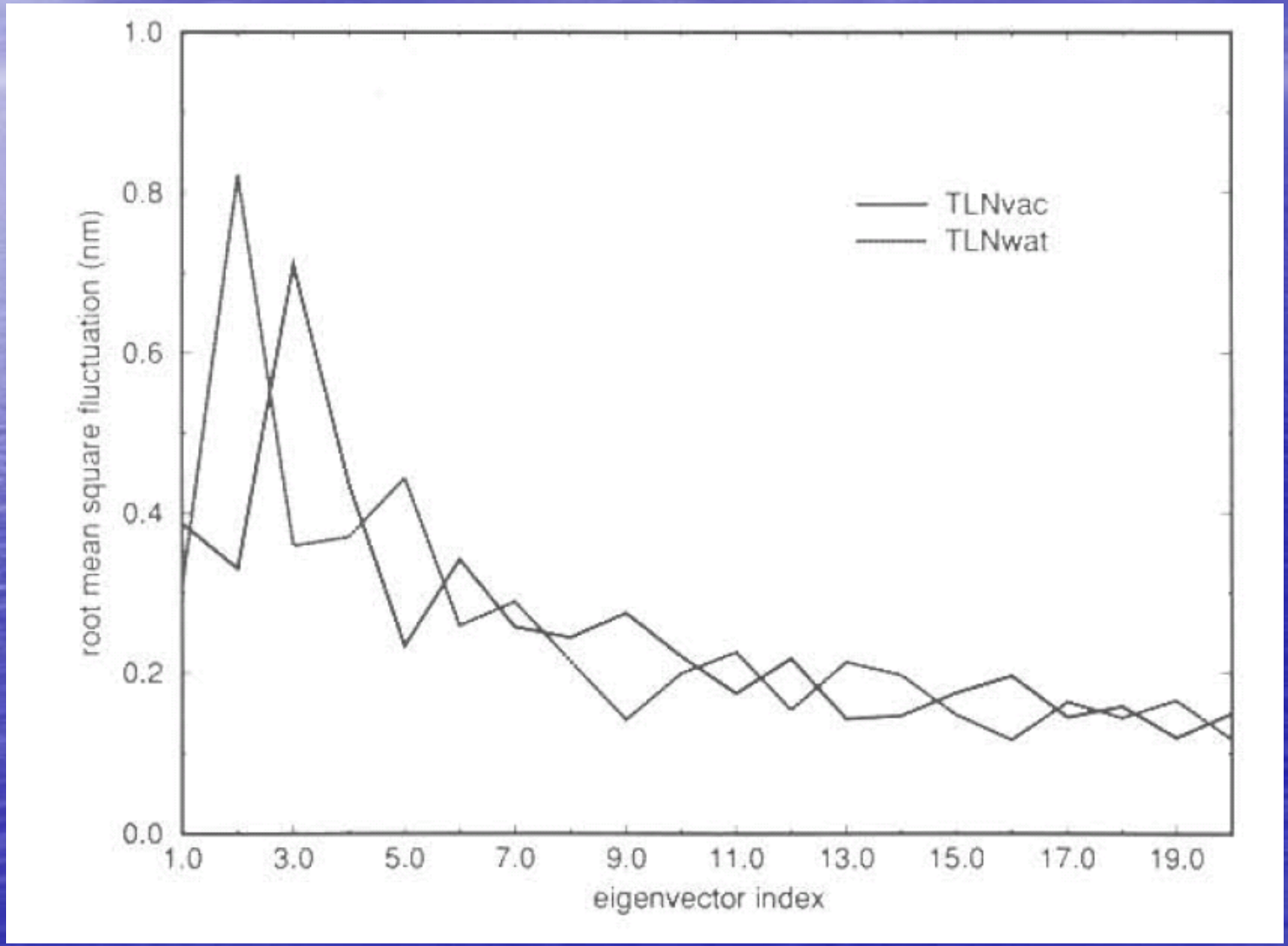
First Four Eigenvector Trajectories



Superposition



Solvent and Vacuum Simulations



Conclusions

- Hinge formation
- Solvent and vacuum simulations

Recent Applications

- Role of platelets in Atherosclerosis and Inflamation - Siegel
  - Mouse model simulation under shear stress
- Combining docking and molecular dynamic simulations in drug design - Alonso
  - MD simulations combined to dock small molecules into protein receptors
- Effects of osmotic pressure in the extracellular matrix on tissue deformation - Lu
  - Solute distribution in the ECM (constant vs. dynamic)

References

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Questions -?-