Computing Transitions from Stable States

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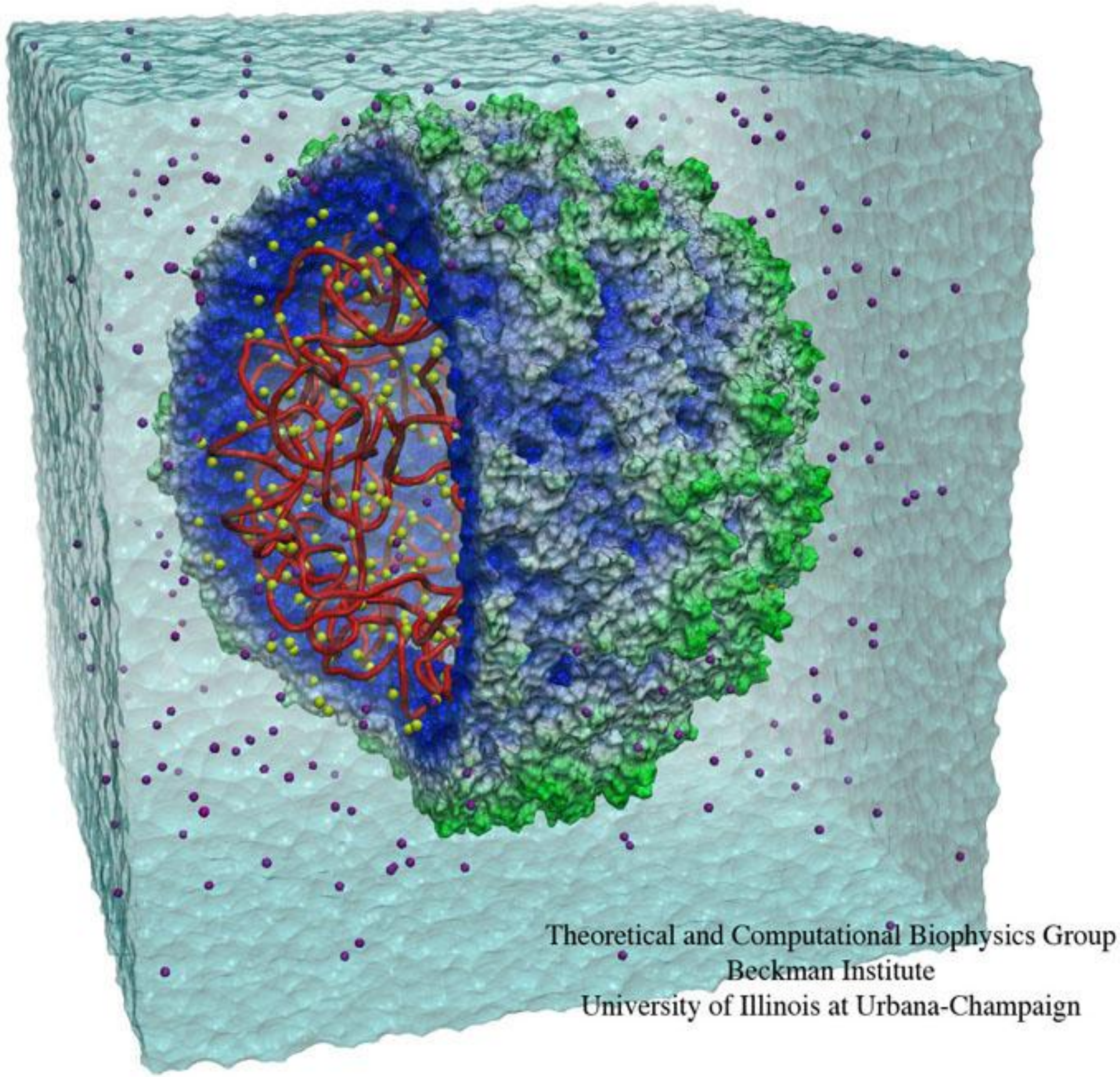
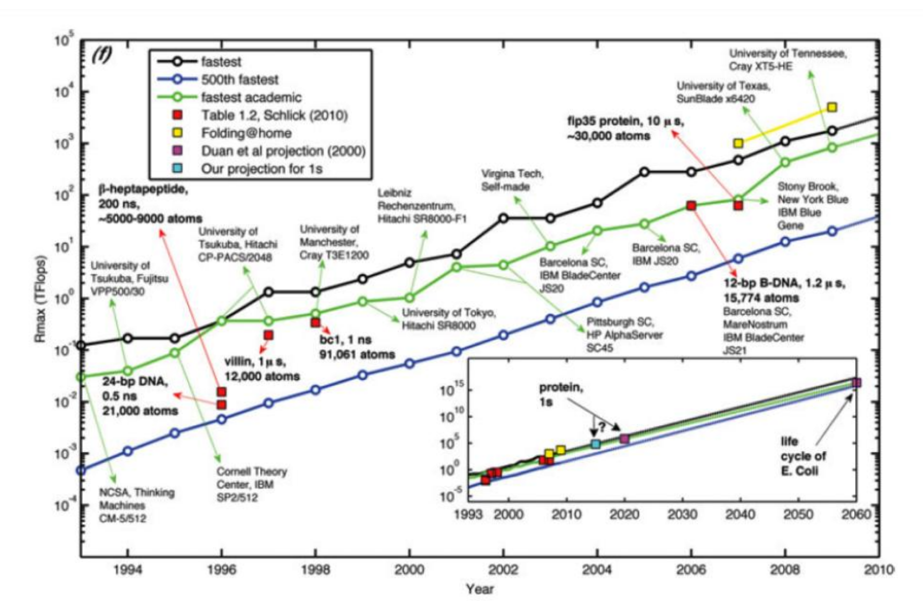
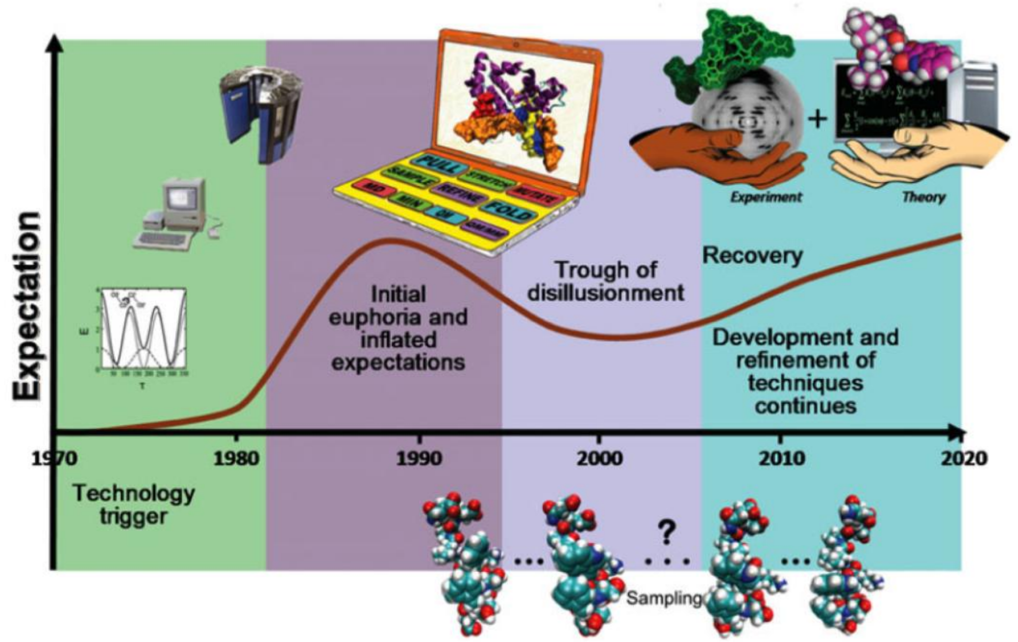
Simulation of Proteins in Native Environments

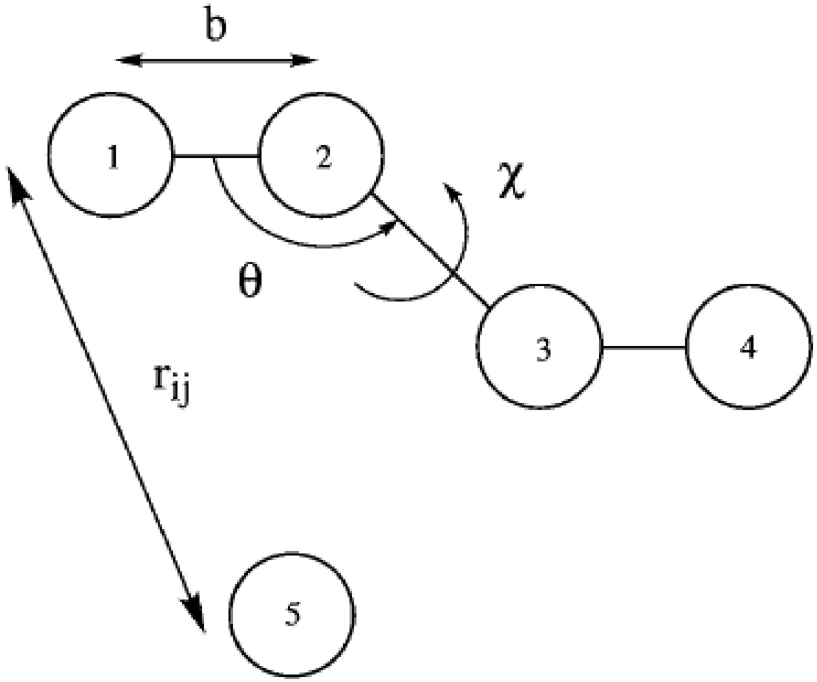


Simulation of Proteins in Native Environments





Dynamic Methods



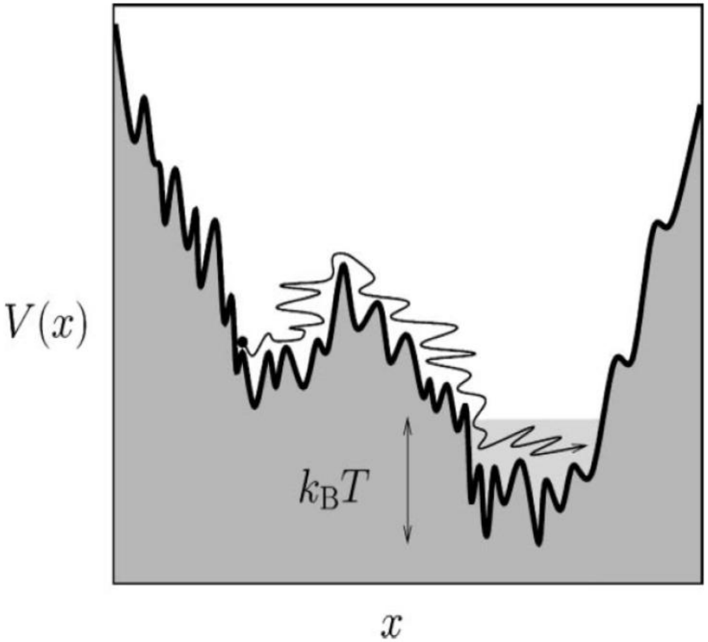
$$F_i = m_i a_i = m_i \ddot{r}_i \qquad F_i = -\nabla_i U(\mathbf{r})$$

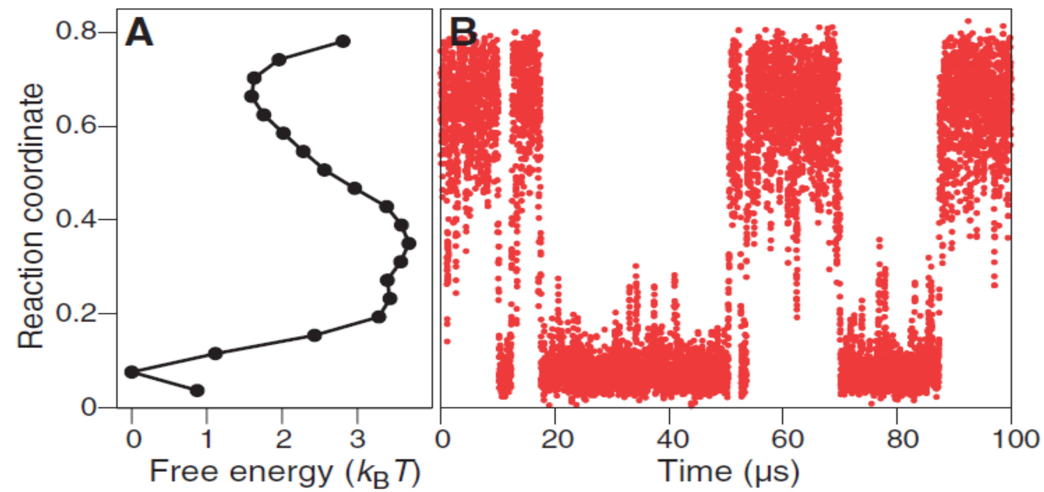
$$V(R)_{\text{total}} = V(R)_{\text{internal}} + V(R)_{\text{external}}$$

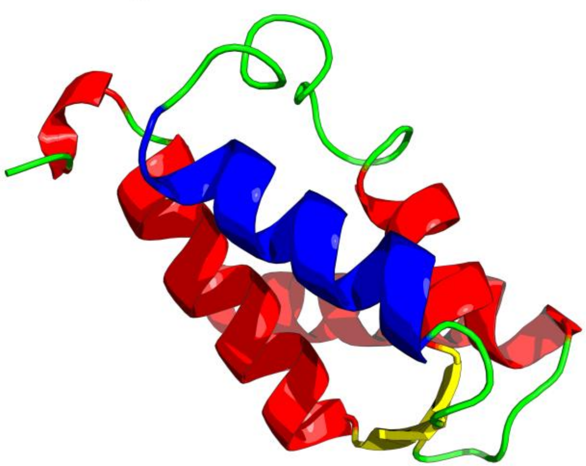
$$V(R)_{\text{internal}} = \sum_{\text{bonds}} K_b(b - b_0)^2 + \sum_{\text{angles}} K_\theta(\theta - \theta_0)^2 + \sum_{\text{dihedrals}} K_\chi[1 + \cos(n\chi - \sigma)]$$

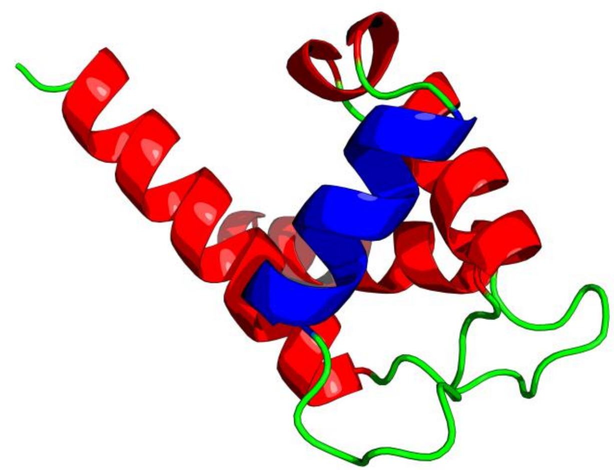
$$V(R)\text{external} = \sum_{\substack{\text{nonbonded}\\ \text{atom pairs}}} \left(\varepsilon_{ij} \left[\left(\frac{R_{\min,ij}}{r_{ij}} \right)^{12} - \left(\frac{R_{\min,ij}}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{\varepsilon_D r_{ij}} \right)$$

Dynamic Methods







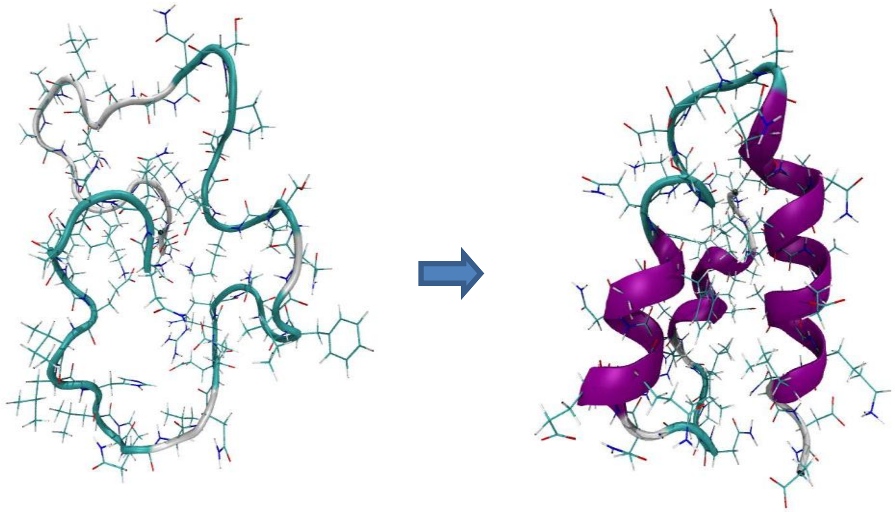


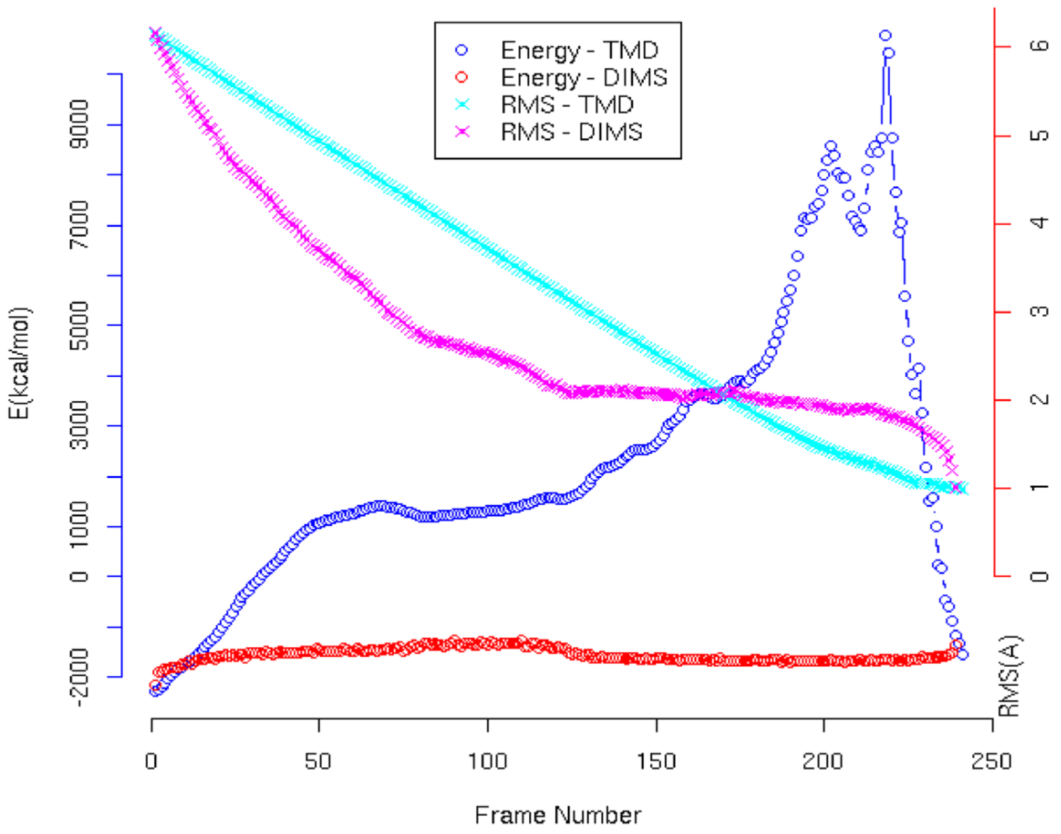
Atomic-Level Characterization of the Structural Dynamics of Proteins, D. E. Shaw et al. *Science* **330,** 341 (2010)

Dynamic Importance Sampling

(DIMS)

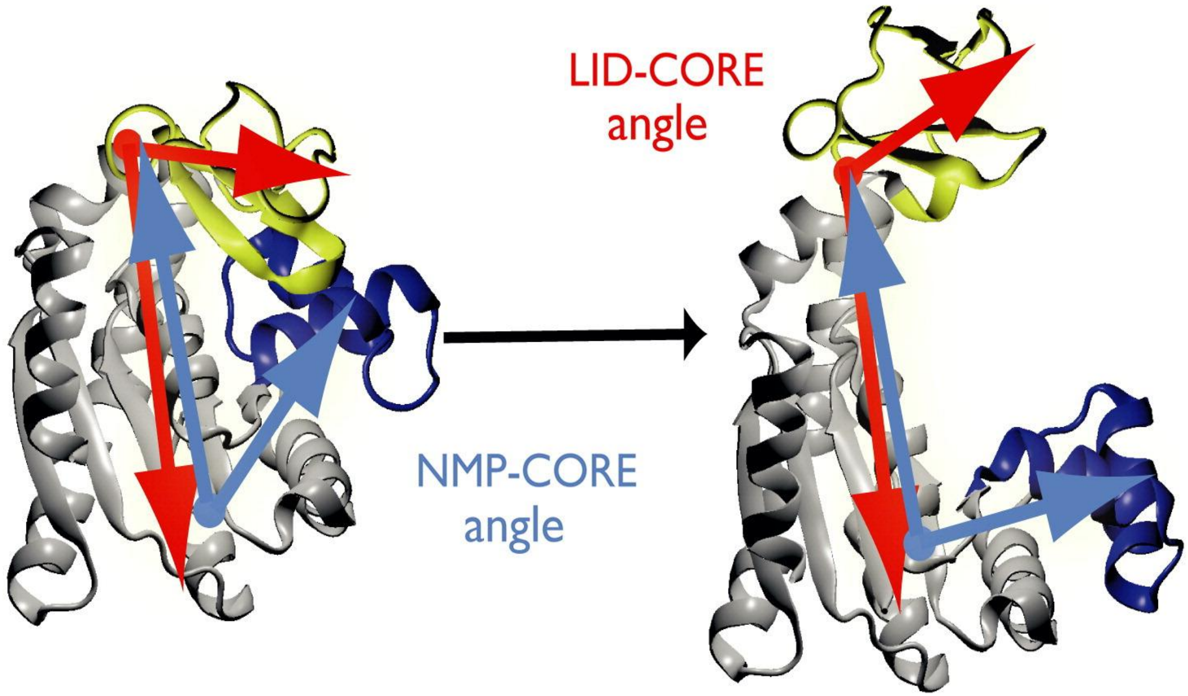
Folding transition of Protein-G





Perilla J., *et al.*, *J. Comp. Chem.* **32**, 196 (2011)

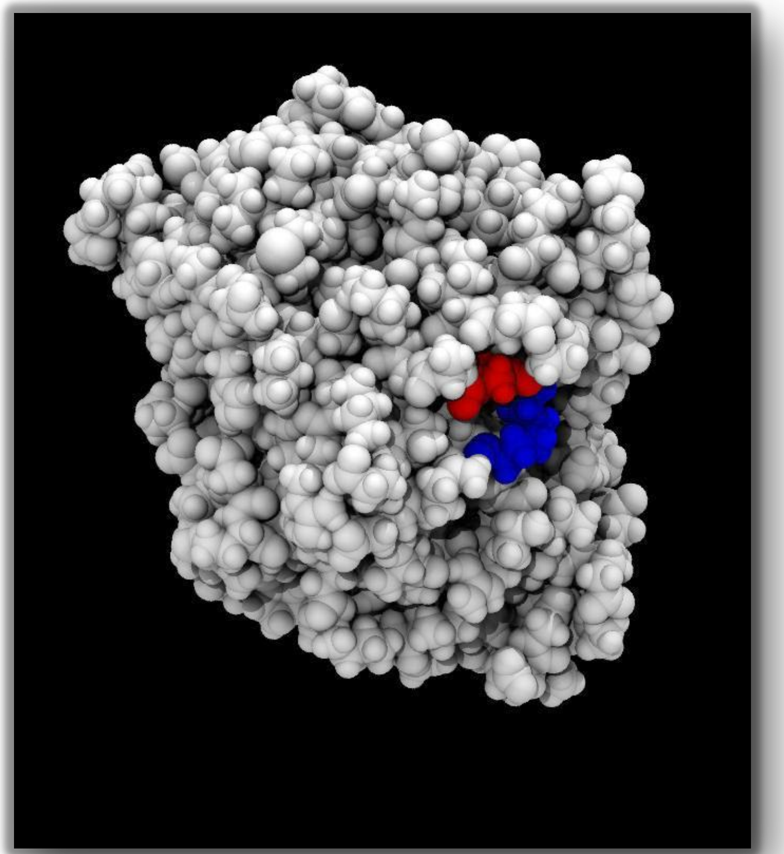
Adenylate Kinase

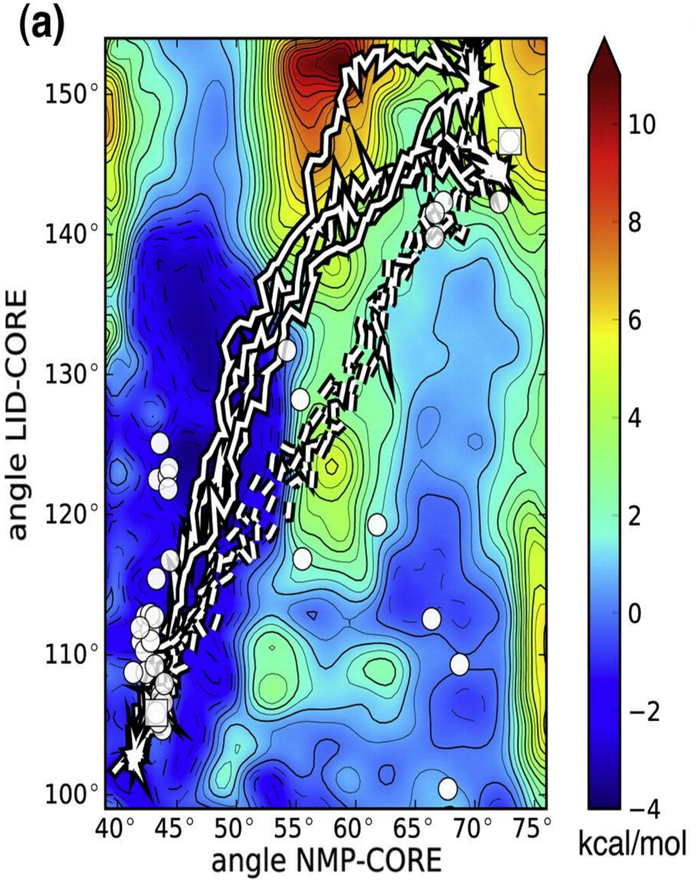


Oliver Beckstein, *Elizabeth Denning, Juan R. Perilla and Thomas B.Woolf*
Journal of Molecular Biology **394**, 150 (2009)

Adenylate Kinase DIMS transition

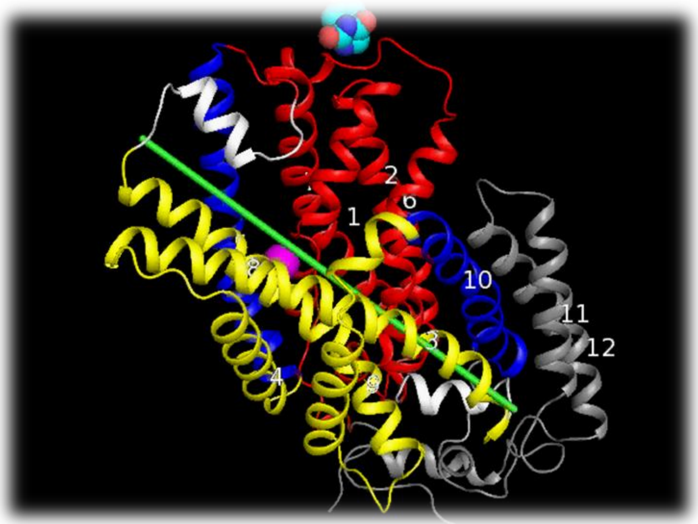
A case of two hinges and a zipping mechanism.

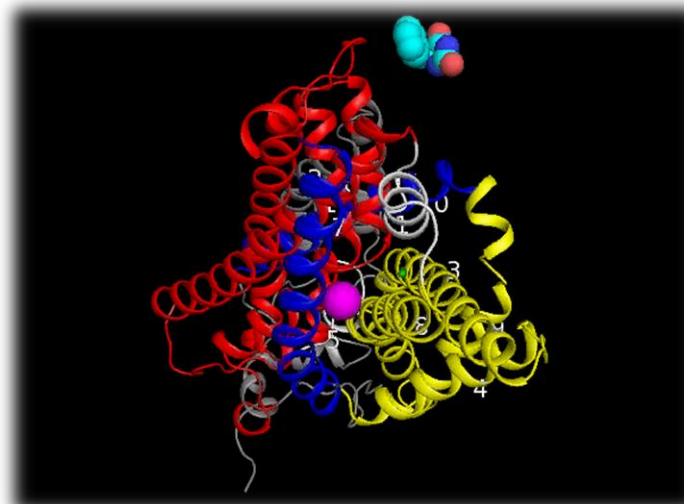


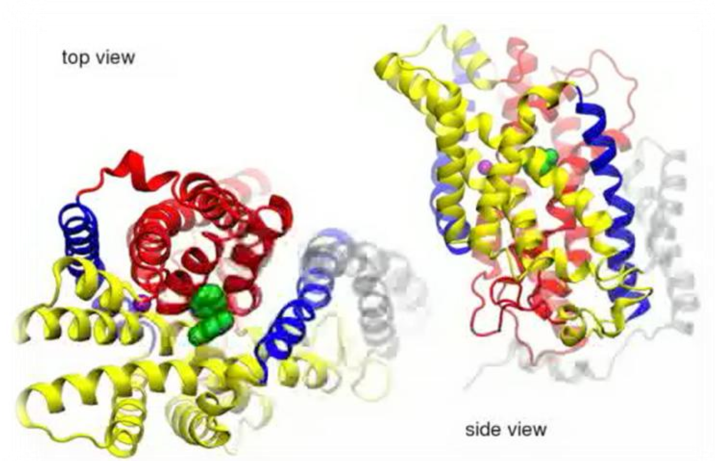


Oliver Beckstein, *Elizabeth Denning, Juan R. Perilla and Thomas B.Woolf*
Journal of Molecular Biology **394**, 150 (2009)

Sodium-Hydantoin Transporter Mhp1





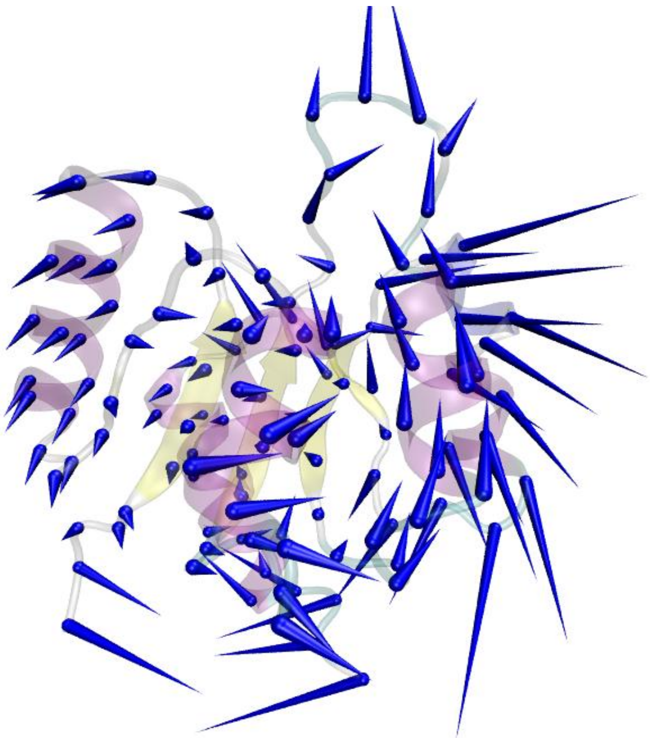


Shimamura, T. et al. *Science* **23,** 470-473 (2010)

Principal Component Analysis

$$\vec{q}(t) = (q_1(t), q_2(t), \ldots, q_{3N}(t)))$$

$$\sigma = \langle (\vec{q}(t) - \langle \vec{q}(t) \rangle)(\vec{q}(t) - \langle \vec{q}(t) \rangle) \rangle$$



Diagonalization problem:

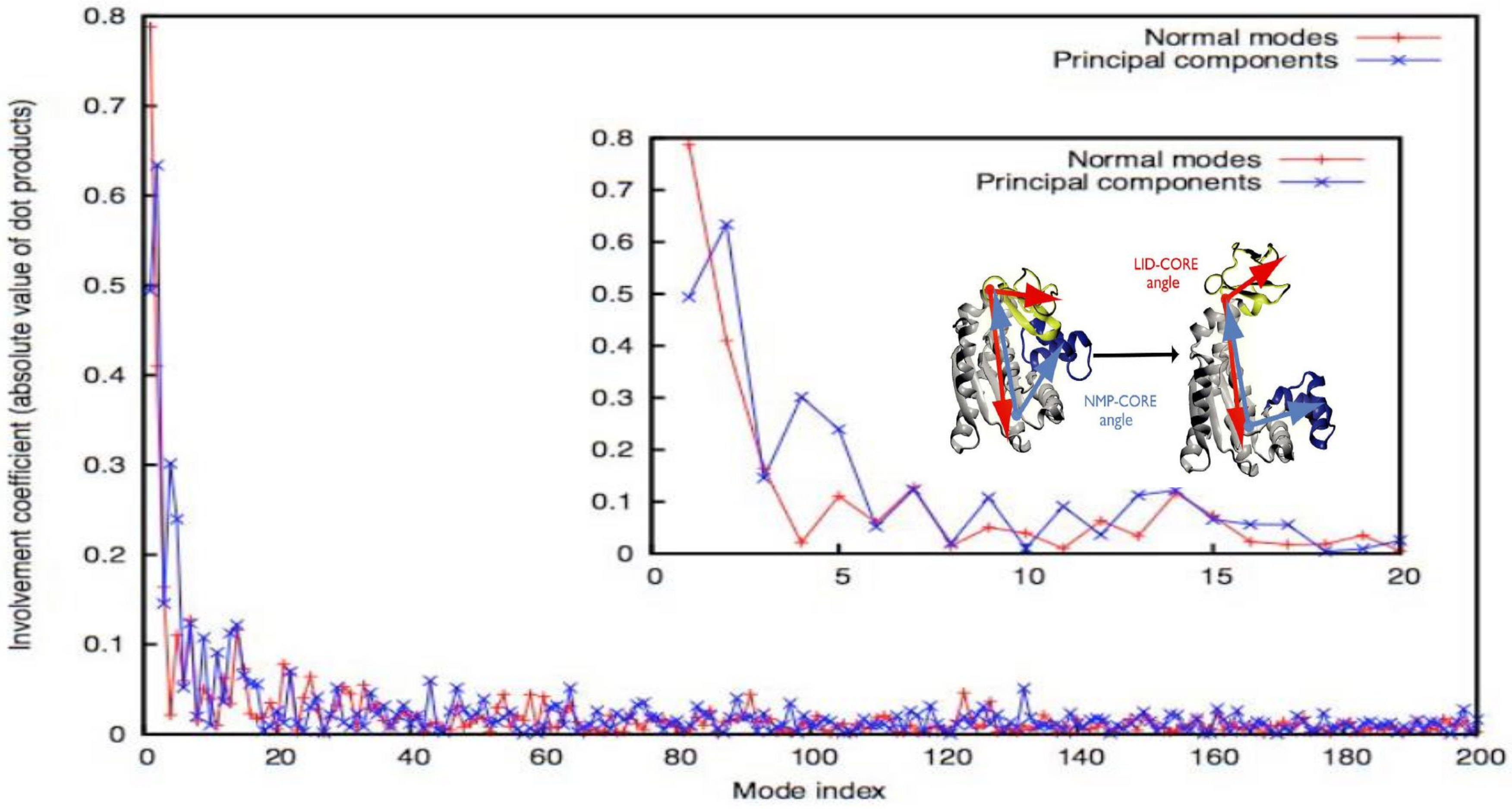
$$\lambda_\alpha \vec{\eta}_\alpha = \sigma$$

Involvement coefficients:

$$\nu_\alpha = ||\vec{\eta}_\alpha \cdot (\hat{q}^A - \hat{q}^B)||$$

NMA and PCA as pathway predictors

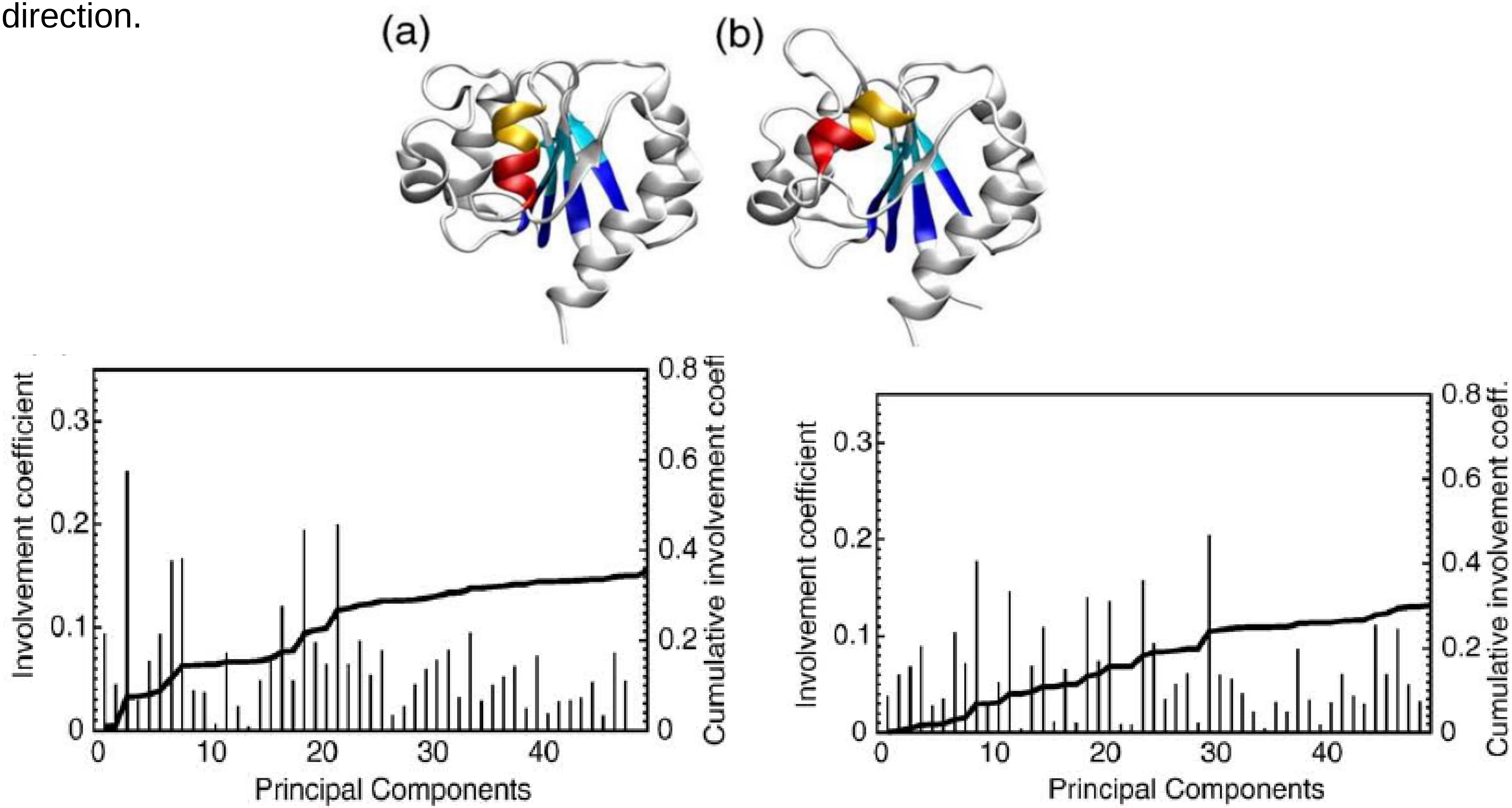
The involvement coefficient indicates the amount of overlap between a PC/NM and a probe direction.



Intrinsinc motions motions along an enzymatic reaction trajectory.
K. A. Henzler-Wildman , *et al*., *Nature* ***450***, 838 (2007)

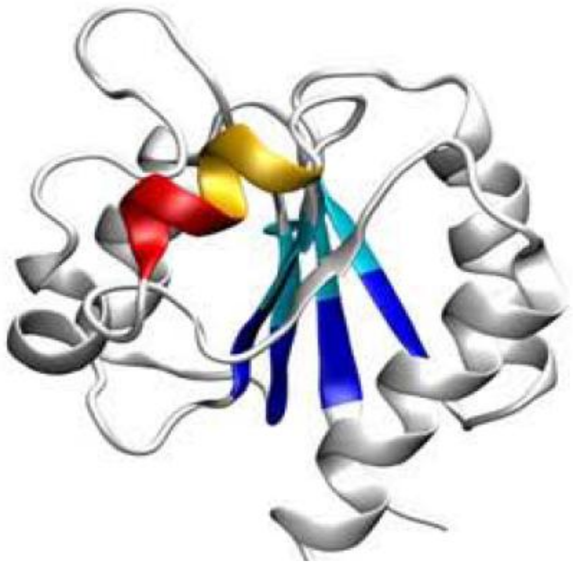
NtrC Principal Component Analysis

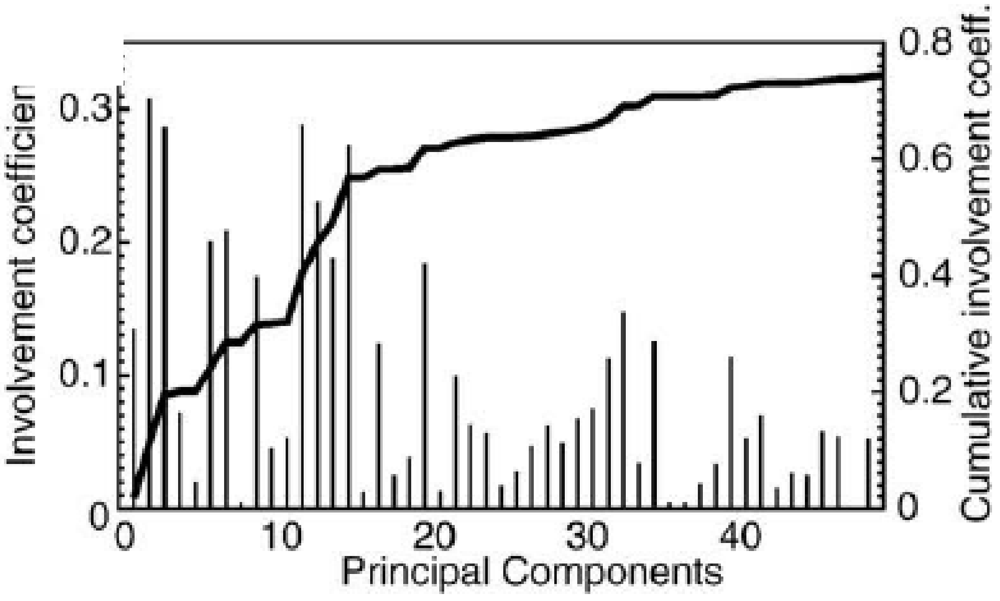
The involvement coefficient indicates the amount of overlap between a PC/NM and a probe direction.

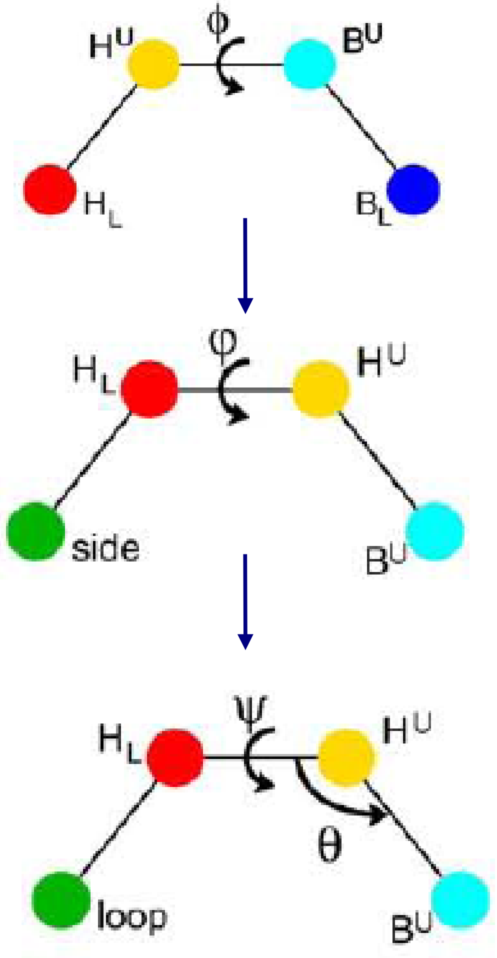


Ming Lei, Dorothy Kern, Martin Karplus., *J. Mol. Bio.* **392**, 823 (2009)

NtrC order parameter

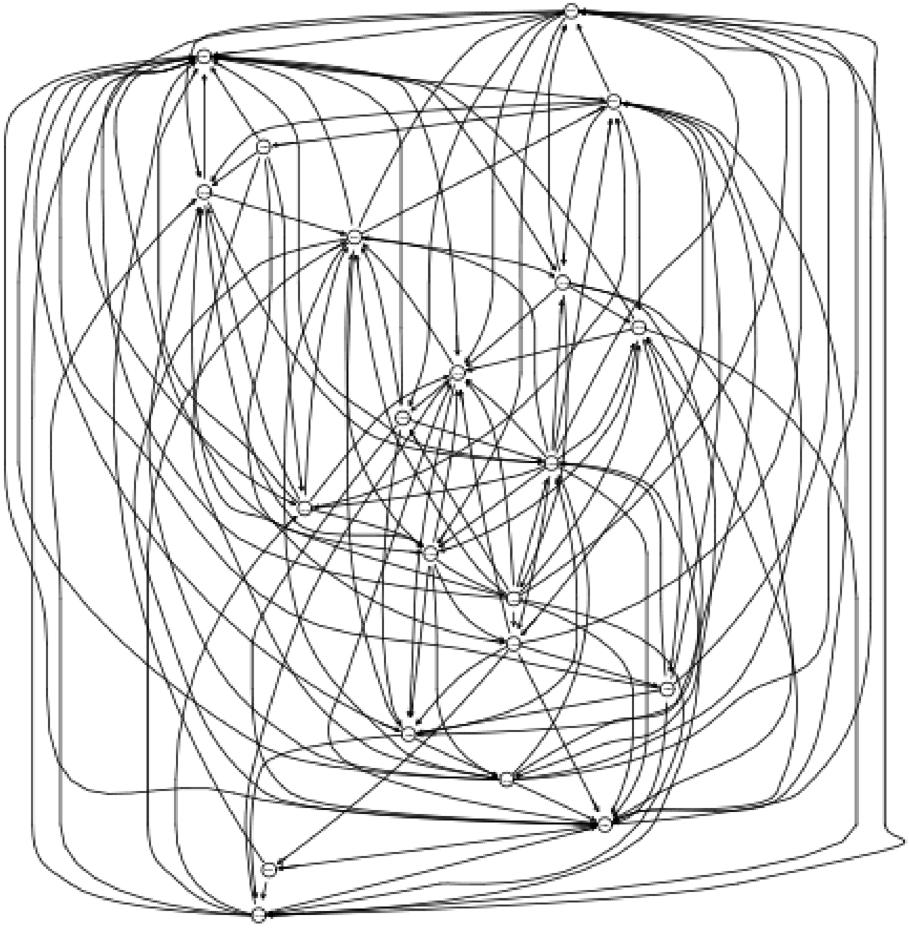






Ming Lei, Dorothy Kern, Martin Karplus., *J. Mol. Bio.* **392**, 823 (2009)

NtrC Transfer entropies



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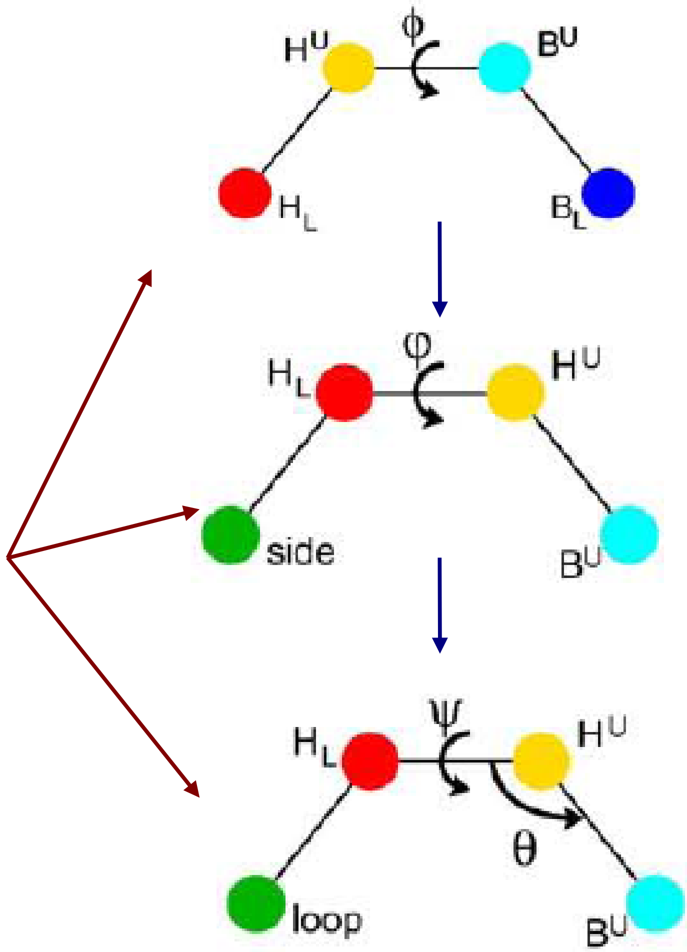


Information Theory Basics

The average number of bits needed to optimally encode independent draws of the discrete variable *X* following a probability distribution *p(x)* is:

$$H(X) = \sum_x p(x) I(x) = -\sum_x p(x) log\left(p(x)\right)$$

If a different distribution *q(x)* is used the excess number of bits is given by the Kullback entropy:

$$K_X = \sum_x p(x) \log\left(\frac{p(x)}{q(x)}\right)$$

Transfer Entropy

Given the generalized Markov property

$$p(x_{n+1}|x_n) = p(x_{n+1}|x_n, y_n)$$

in the absence of information flow from X to Y, the state of Y has no influence on the transition probabilities on system X. The incorrectness of this assumption can be quantified by a Kullback entropy:

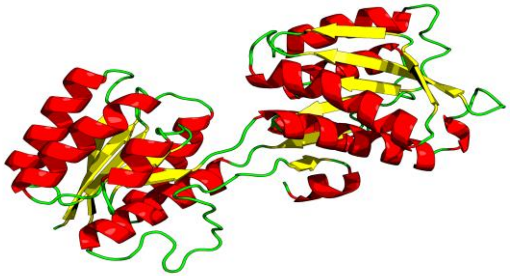
$$T_{X\to Y} = \sum p(x_{n+1}, x_n, y_n) \log \frac{p(x_{n+1}|x_n, y_n)}{p(x_{n+1}|x_n)}$$

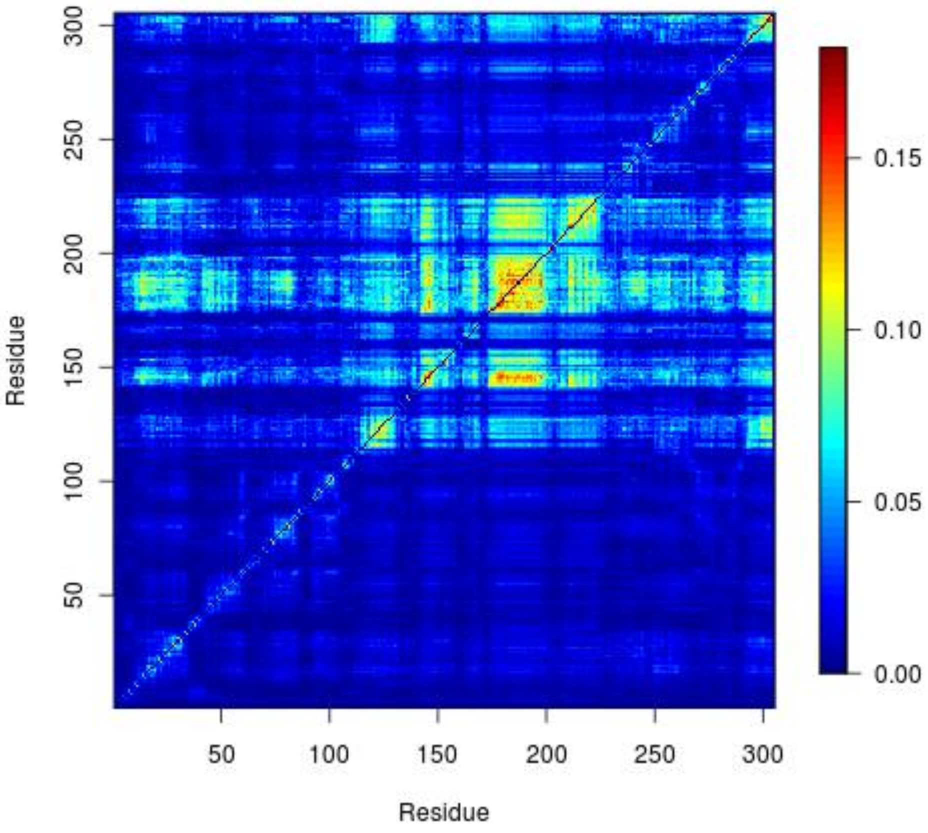
$$T_{Y\to X} = \sum p(y_{n+1}, y_n, x_n) \log \frac{p(y_{n+1}|y_n, x_n)}{p(y_{n+1}|y_n)}$$

Thomas Schreiber, *Phys. Rev. Lett.* **85**, 461 (2000)

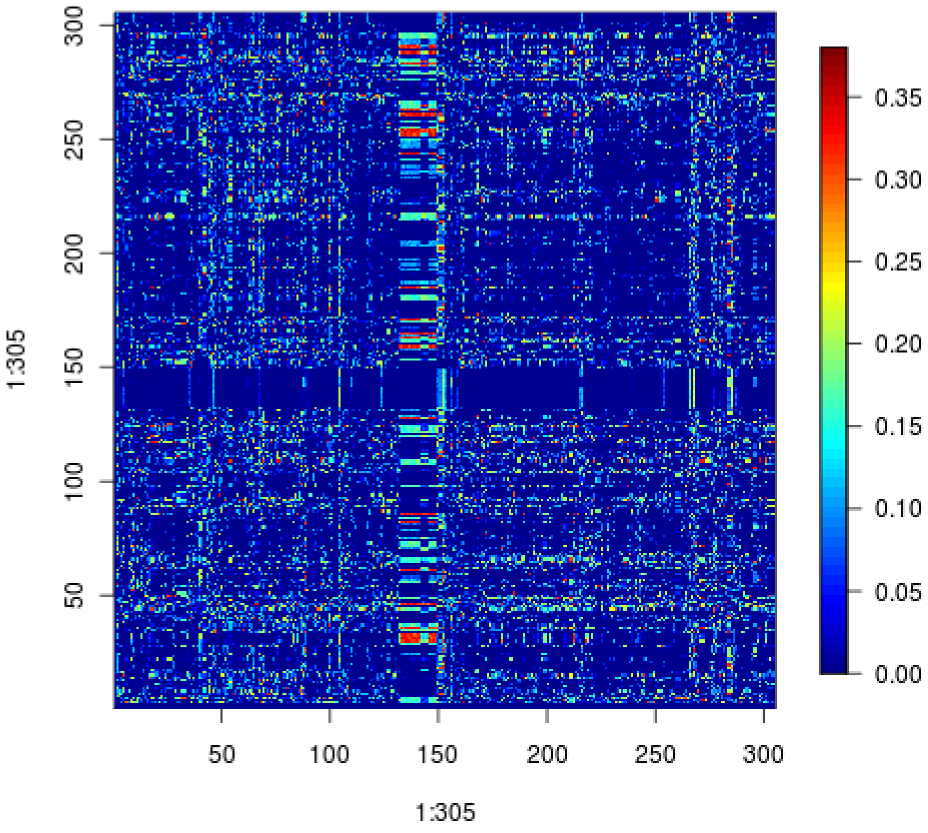
Transfer Entropies for GGBP

DIMS Transition

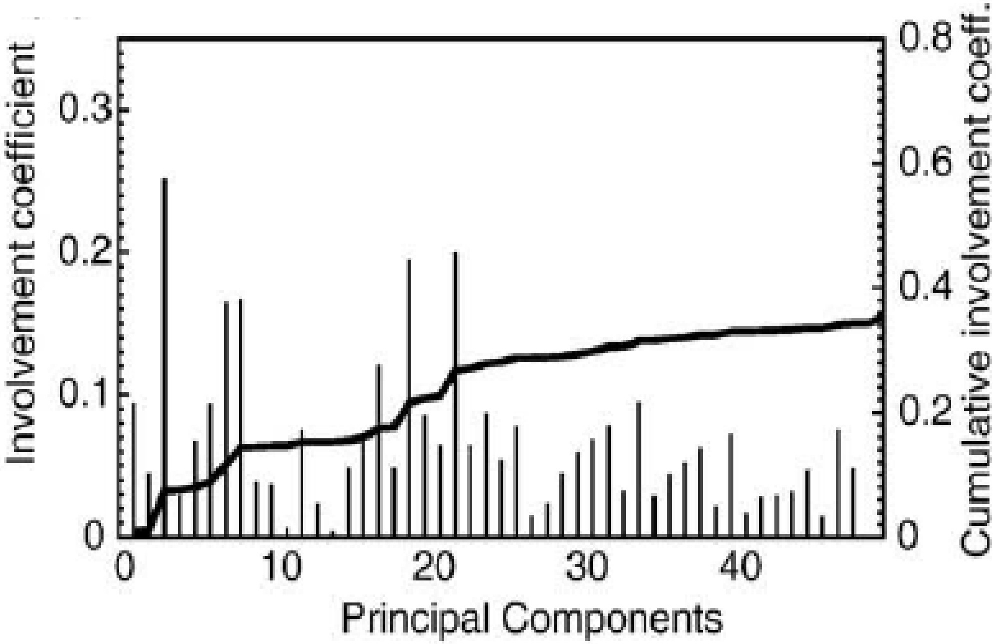


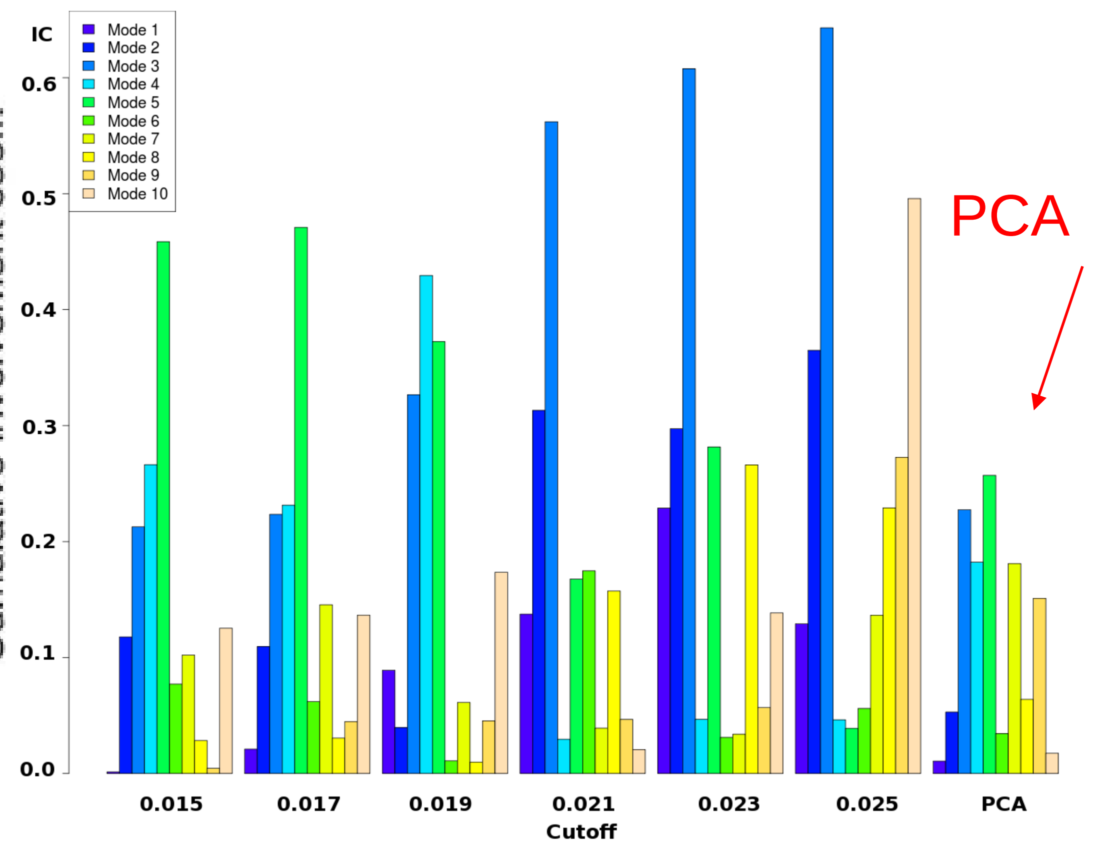


GGBP pulling 20nN Wavelet level = 4



PCA - Involvement Coefficient

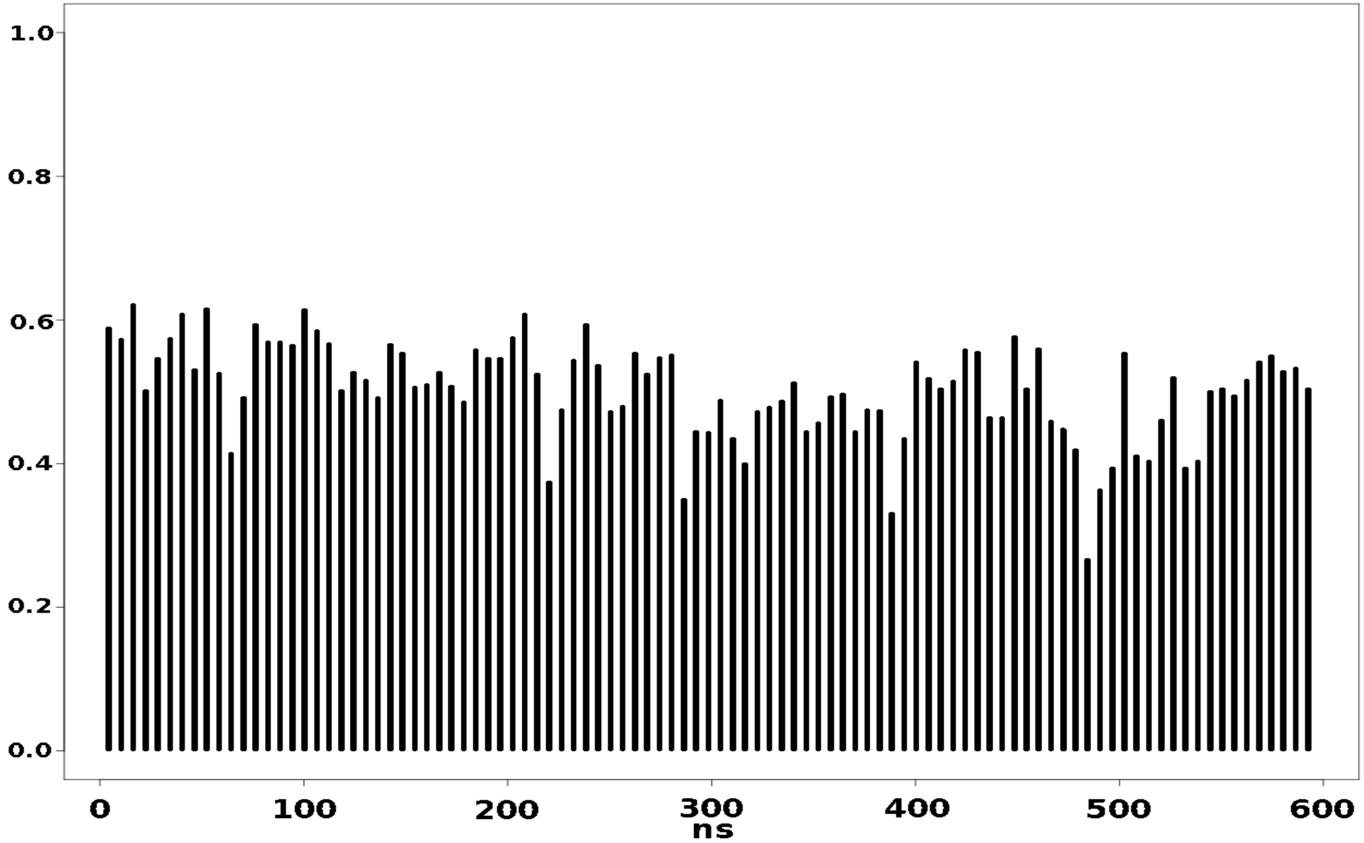




$$\lambda_\alpha \vec{\eta}_\alpha = \sigma \qquad \nu_\alpha = ||\vec{\eta}_\alpha \cdot (\hat{q}^A - \hat{q}^B)||$$

PCA – Cumulative Involvement Coefficient

$$\nu_\alpha = \|\vec{\eta}_\alpha \cdot (\hat{q}^A - \hat{q}^B)\| \qquad \mu_\alpha = \sum_{i=1}^{\alpha} \nu_i^2$$



Future Steps

- **NAMD** supports **GPU** acceleration since **2007**
- Enhanced sampling techniques are currently under development.
- Implicit solvation models allow for the simulation of even larger systems.

NAMD SC Paper:

Thursday Nov **17**th
11:00am.
Room: **TCC 304**

For more information please visit:

http://www.ks.uiuc.edu/

Questions:
juan@ks.uiuc.edu