Hands-on Workshop on Computational Biophysics

by

The Theoretical and Computational Biophysics Group (TCBG)

and

The National Center for Multiscale Modeling of Biological Systems (MMBioS)

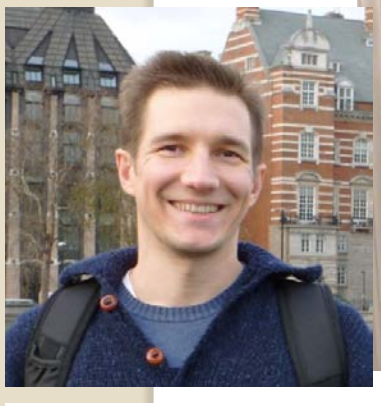
ProDy

Protein Dynamics Analysis in Python

NMWiz

Dr. Ying Liu

Cihan Kaya



Dr. Timothy R Lezon
Assistant Prof, DCSB, Pitt

Drs. Ahmet Bakan and Anindita Dutta

Dr. Chakra Chennubhotla
Assist Prof, DCSB, Pitt

Reference:

Bakan A, Meireles LM, **Bahar I**. (2011) ProDy: Protein dynamics inferred from theory and experiments *Bioinformatics* **27**:1575-7

Bakan, A., Dutta, A., Whenzi, M., Liu, Y., Chennubhotla, C., Lezon, T.R., & Bahar, I. (2014) *Bioinformatics* in press.

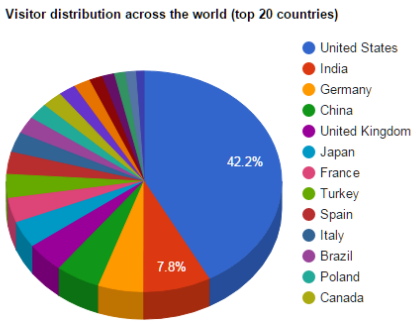
ProDy References

Bakan A,* Dutta A,* Mao W, Liu Y, Chennubhotla C, Lezon TR, Bahar I (2014) Evol and ProDy for Bridging Protein Sequence Evolution and Structural Dynamics *Bioinformatics* **30**: 2681-3

Bakan A, Meireles LM, Bahar I (2011) ProDy: Protein dynamics inferred from theory and experiments *Bioinformatics* **27**: 1575-1577.

ProDy: Usage and dissemination statistics

Date	Releases	Downloads[1]	Visits[2]	Unique[3]	Pageviews[2]	Countries[5]
Nov '10 – Oct '11	19	8,530	8,678	2,946	32,412	45
Nov '11 – Oct '12	6+9*	35,108	16,472	6,414	71,414	59
Nov '12 – Oct '13	8*	87,909	19,888	8,145	86,204	66
Nov '13 – Oct '14	5*	140,101	24,134	11,170	112,393	69
Nov '14 – May '15	1*	68,230	15,941	8,479	66,641	50
June '15 – June '16	5*	124,613	32,491	15,402	140,818	132
Total	**53**	**464,491**	**117,604**	**52,556**	**509,882**	**132**



* Indicates software release made during the grant period.

[1] Download statistics retrieved from PyPI (https://pypi.python.org/pypi/ProDy) (https://pypi.python.org/pypi/vanity).

Google Analytics (www.google.com/analytics) was used to track:

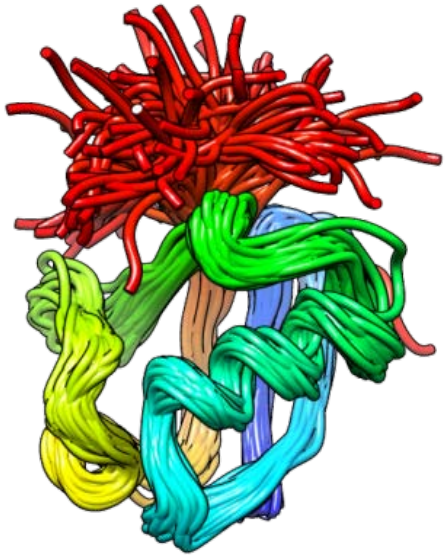
[3] Unique indicates number of unique visitors;

[5] Country of origin for visits.

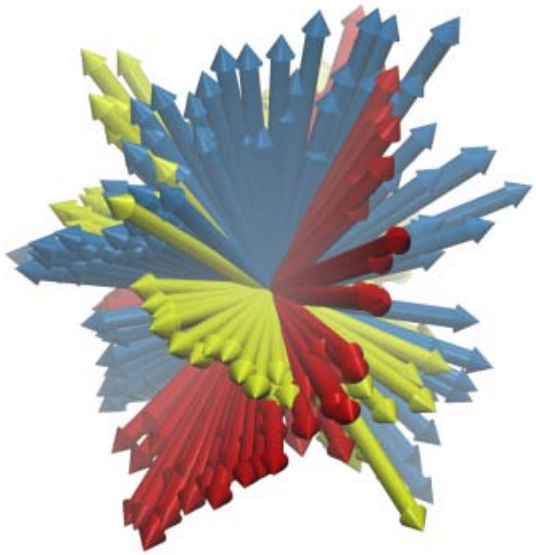
Tutorials

Day 4

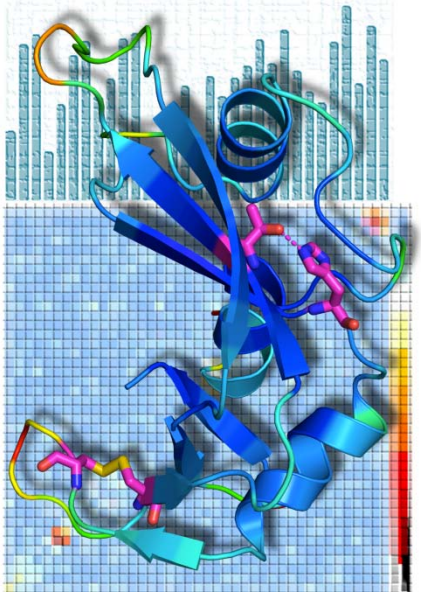
http://prody.csb.pitt.edu/tutorials/



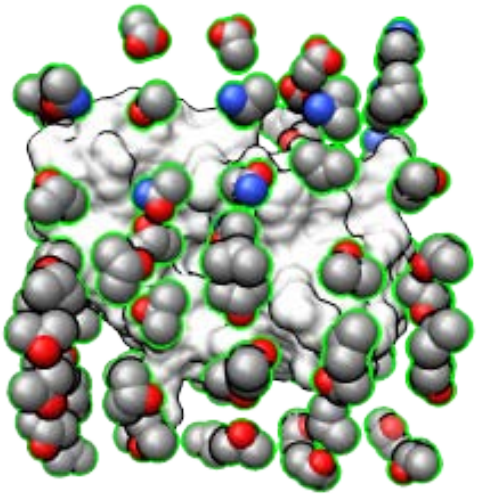
ProDy



NMWiz



Evol



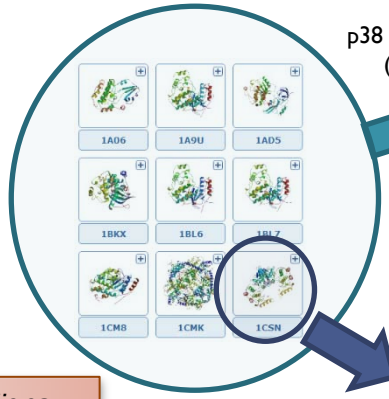
Druggability

ProDy for exploring conformational space

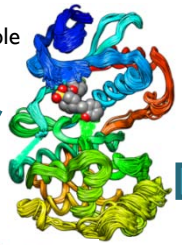
Protein Dynamics Analysis in Python

User inputs a protein sequence

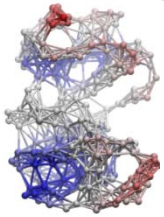
>1A9U:A|PDBID|CHAIN
GSSHHHHHHSSGLVPRGSHMSQER
PTFYRQELNKTIWEVPERYQNLSPV
GSGAYGSVCAAFDTKTGLRVAVKK
LSRPFQSIIHAKRTYRELRLLKHMKH
ENVIGLLDVFT.....

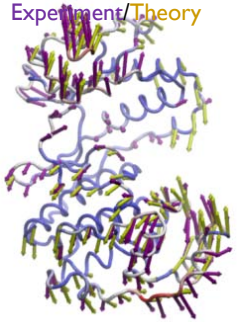


p38 ensemble (PCA)

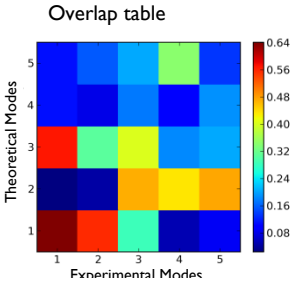


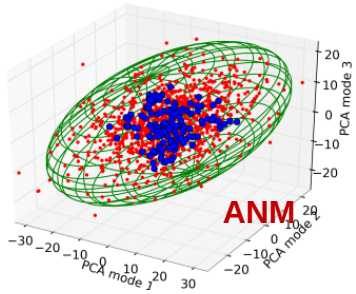
p38 network model (ANM)



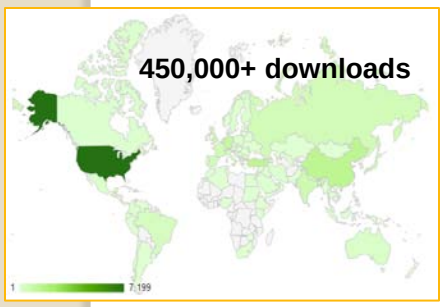


User can compare experimental and theoretical models

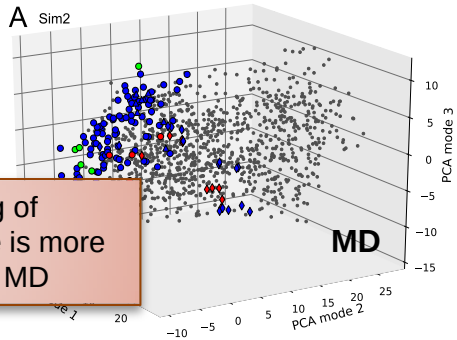




ProDy *identifies*, *retrieves*, *aligns,* and *analyzes (PCA)* structures that match the input sequence



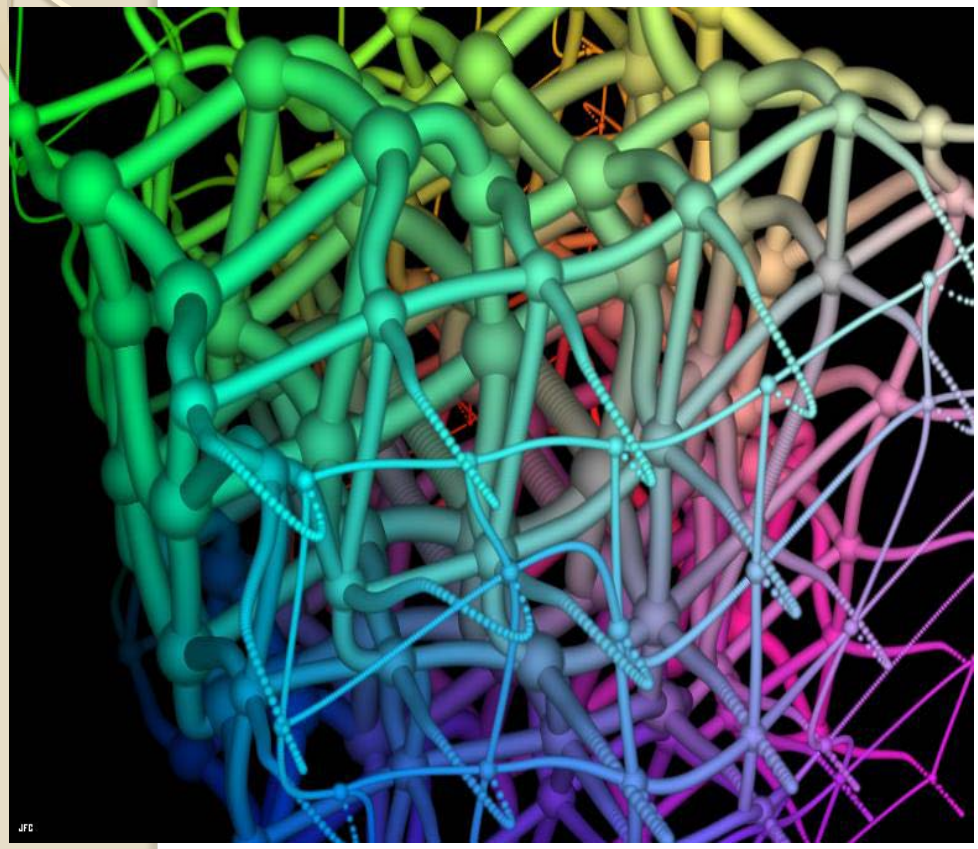
Source http://www.google.com/analytics/



ProDy-ANM sampling of conformational space is more complete than that of MD

User can sample an ensemble of conformations along ANM modes for docking simulations

Representation of structure as a network



http://www.lactamme.polytechnique.fr/

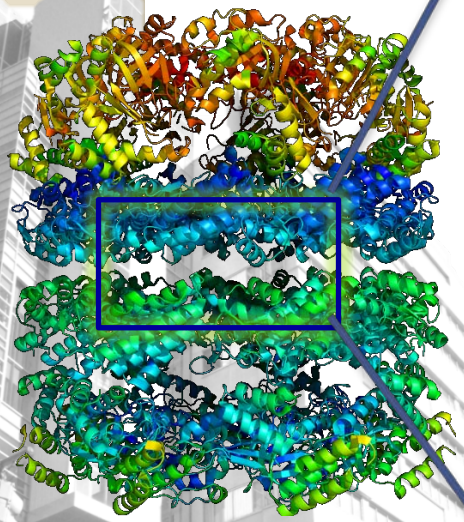
Why network models?

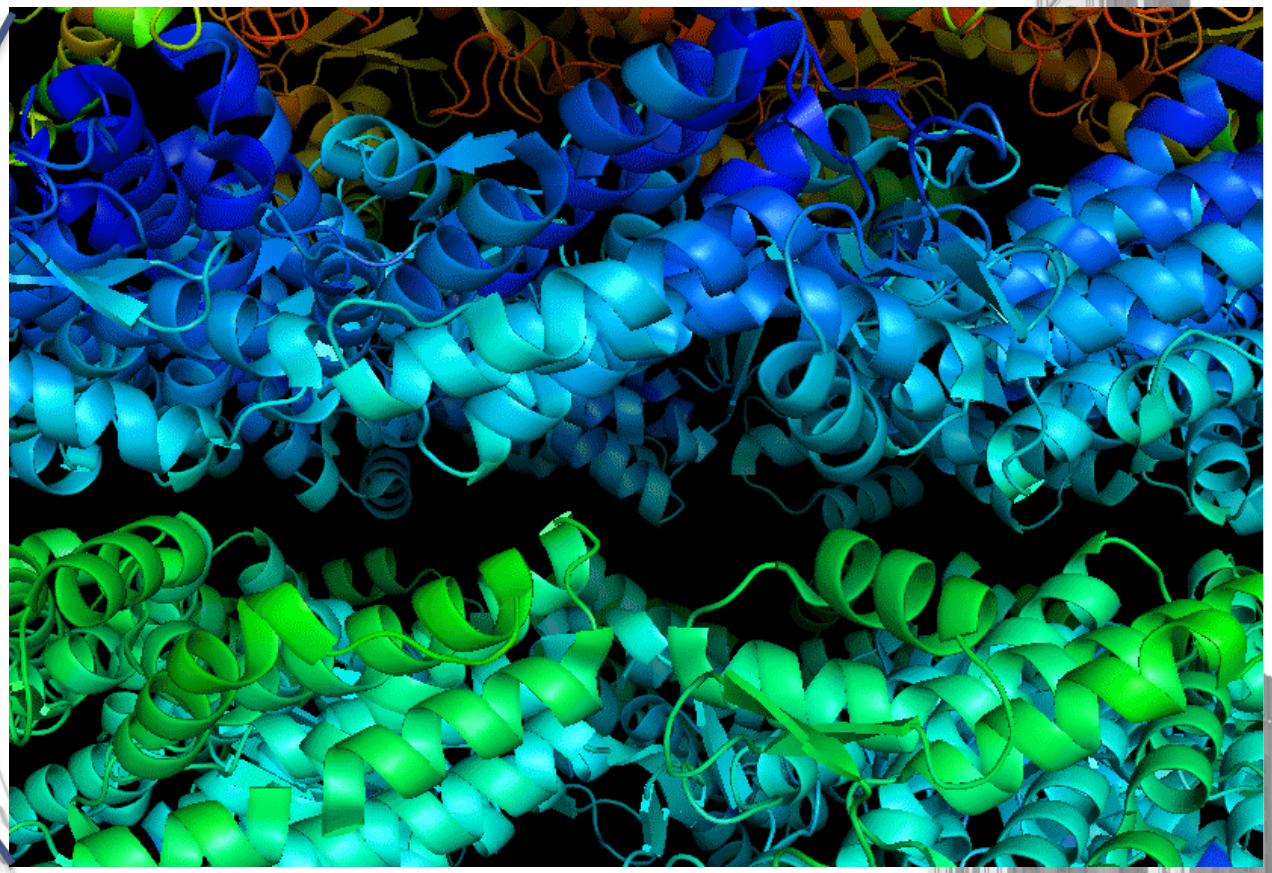
- for large systems' collective motions & long time processes beyond the capability of full atomic simulations
- to incorporate structural data in the models – at multiple levels of resolution
- to take advantage of theories developed in other disciplines: polymer physics, graph theory, spectral graph methods, etc.

Major advantages of ProDy:

- Visualizing the global dynamics
- Applicability to large systems
- Assessing cooperative motions
- Efficiency – immediate results
- Relevance to observables

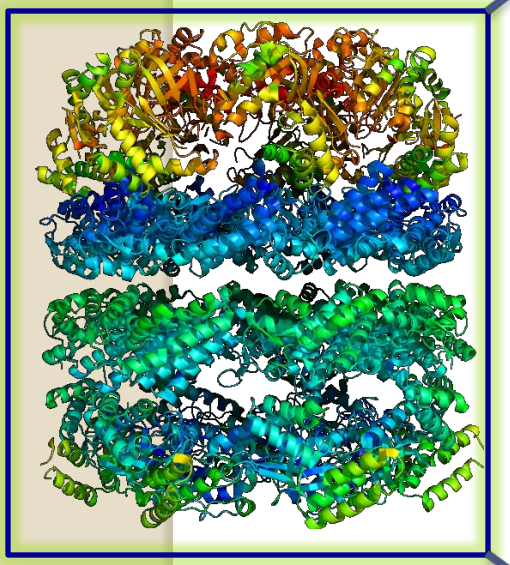
Proteins are not static:
They move, breath, work, dance, interact with each other

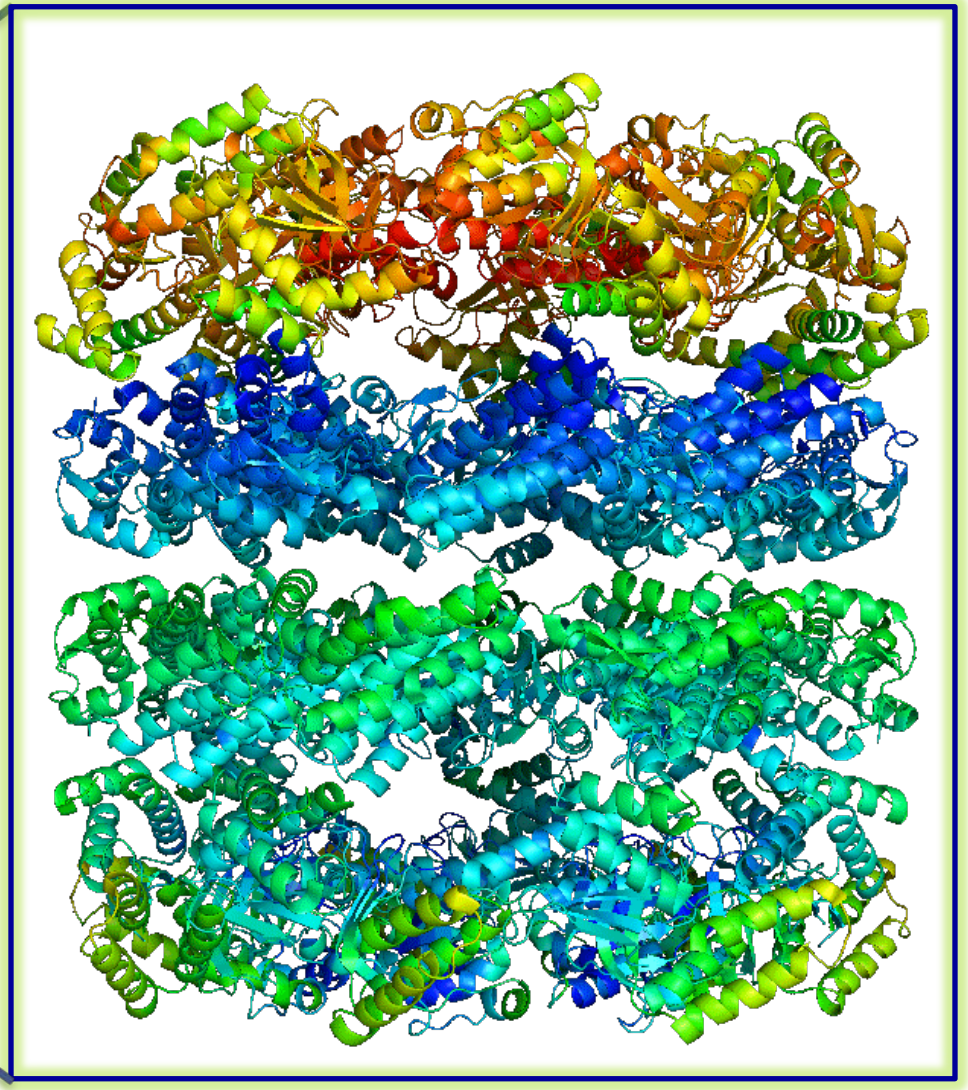




Local motions

Proteins are not static:
They move, breath, work, dance, interact with each other

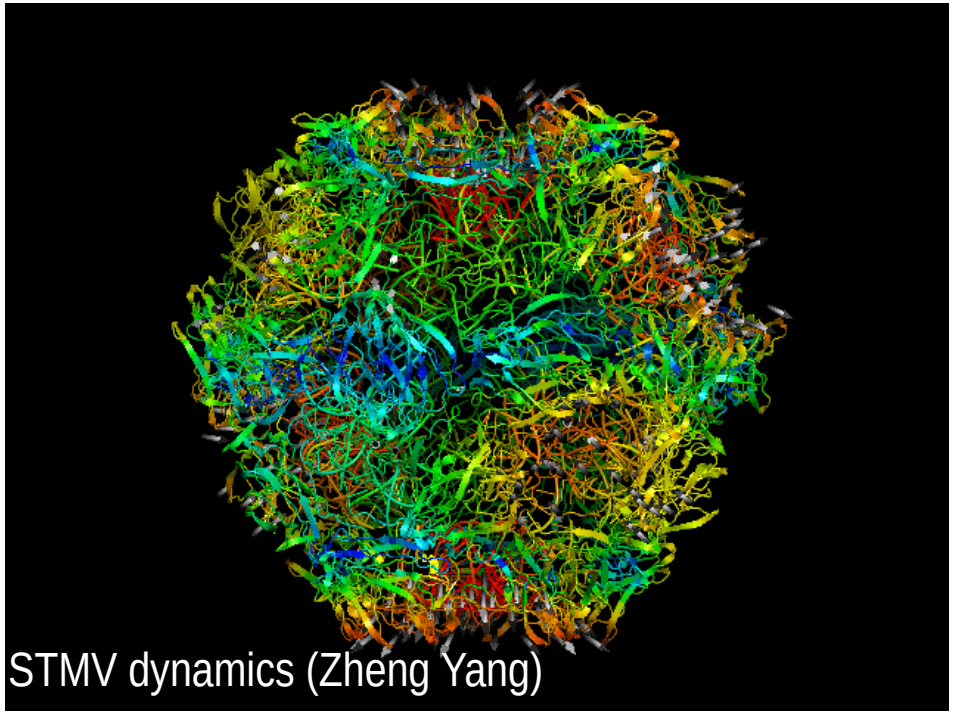




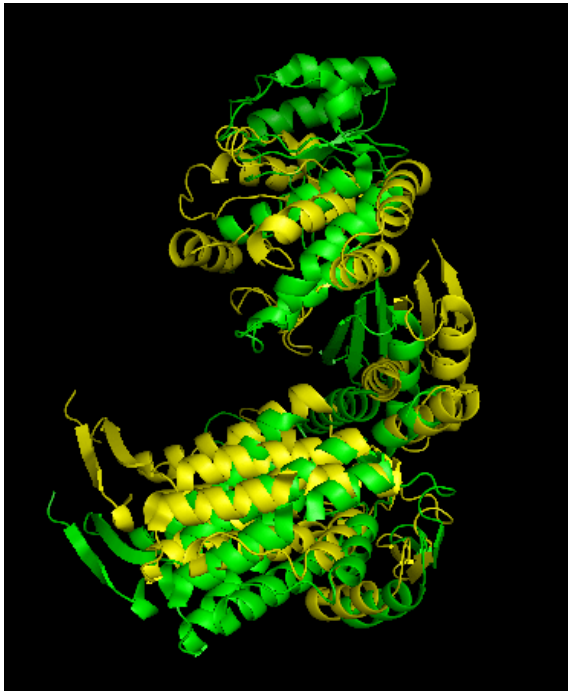
Global motions

Many proteins are molecular machines

And mechanical properties become more important in complexes/assemblies



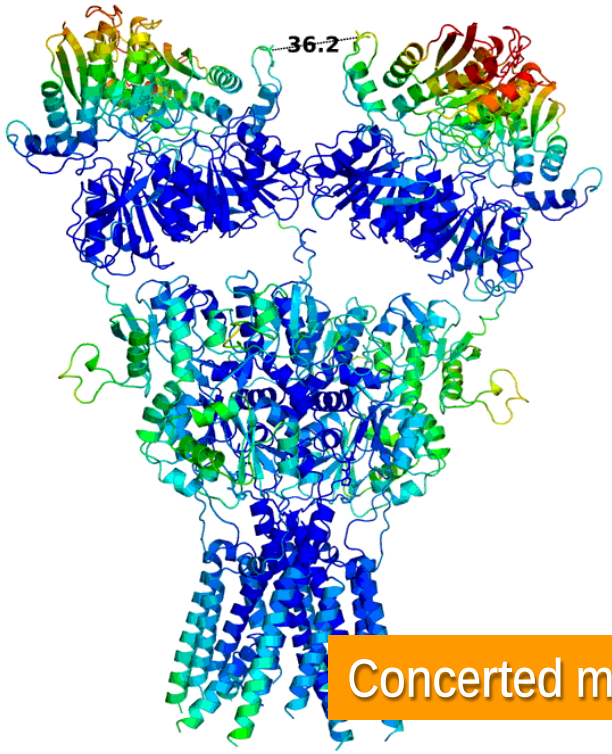
STMV dynamics (Zheng Yang)

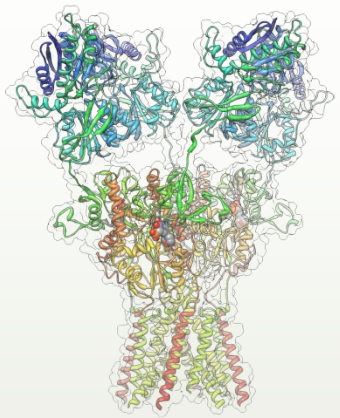


Each structure encodes a unique dynamics

Structure → Dynamics → Function

Signaling dynamics of AMPARs and NMDARs





domain/subunit motions

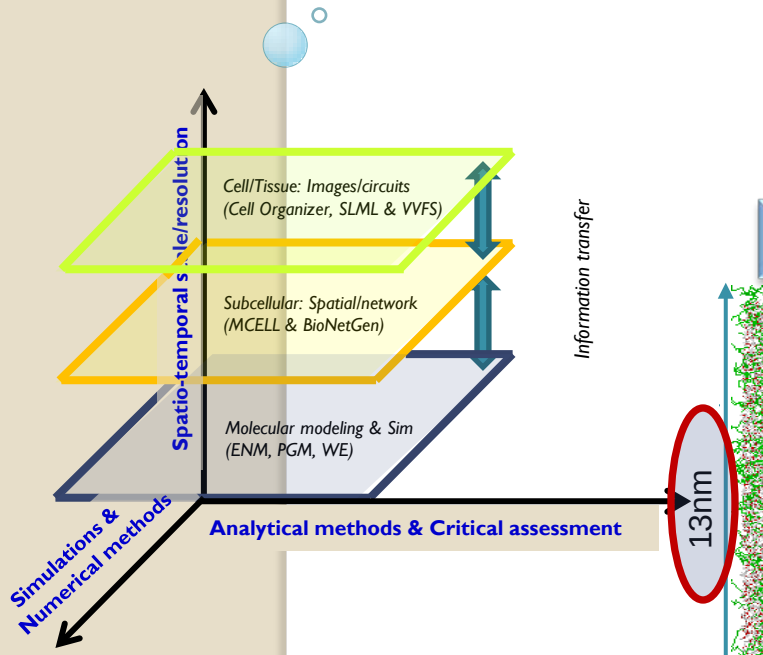
Concerted movements of signaling molecules

Dutta A, Krieger J, Lee JY, Garcia-Nafria J, Greger IH, Bahar I (2015) Cooperative Dynamics of Intact AMPA and NMDA Glutamate Receptors: Similarities and Subfamily-Specific Differences *Structure* **23**: 1692-170

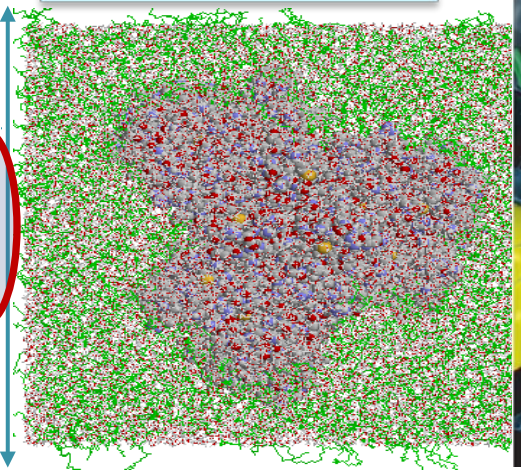
GOAL: TO GENERATE DATA FOR MESOSCOPIC SCALE

Developing integrated *methodology to enable information transfer across scales*

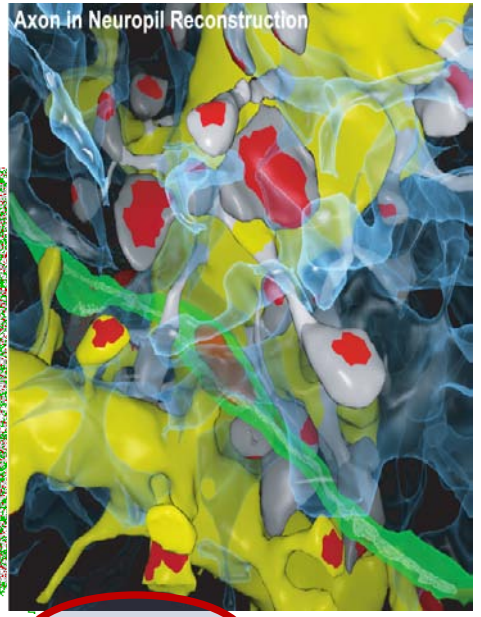
Microphysiological simulations



from molecules



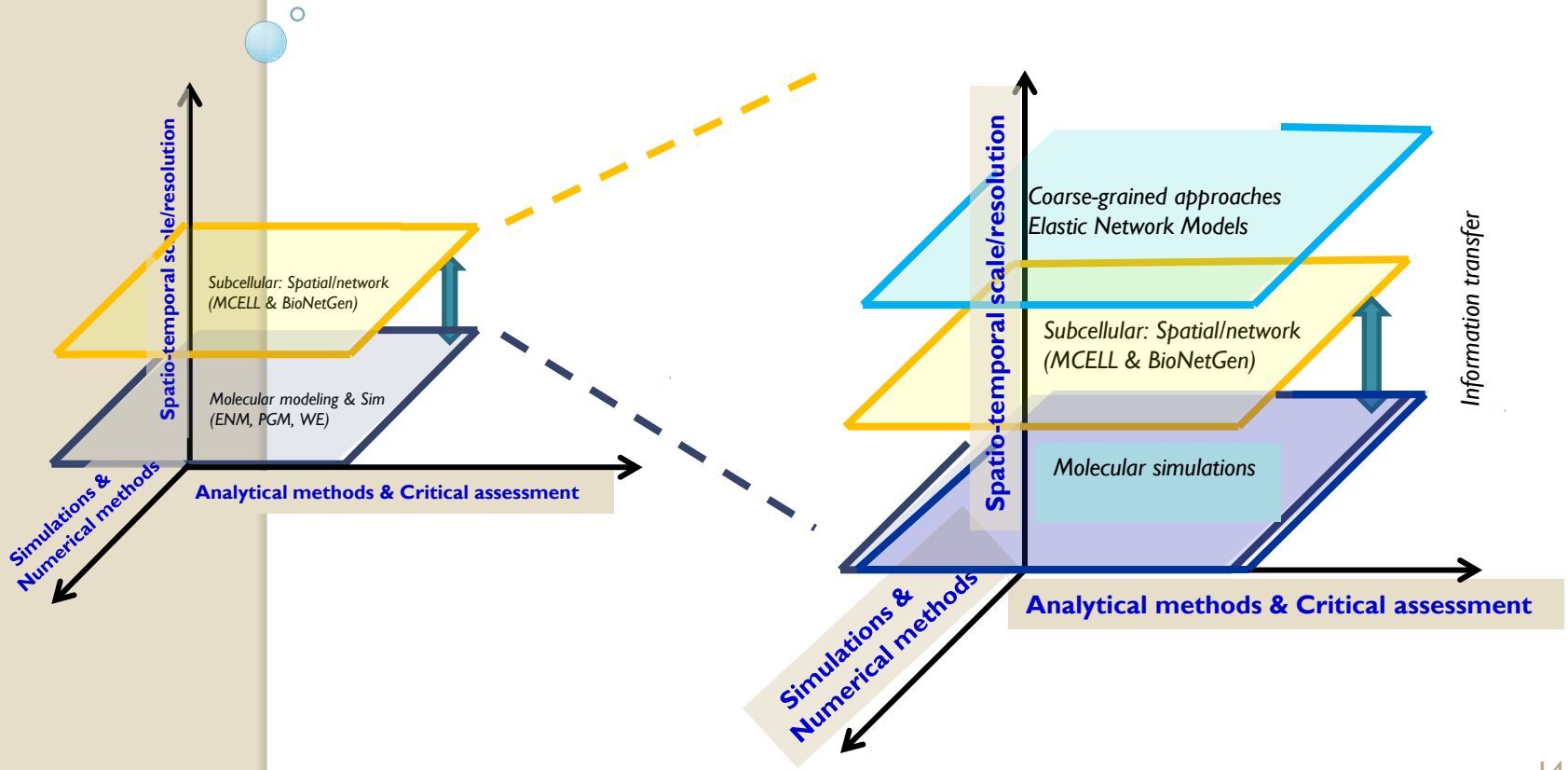
to subcellar events



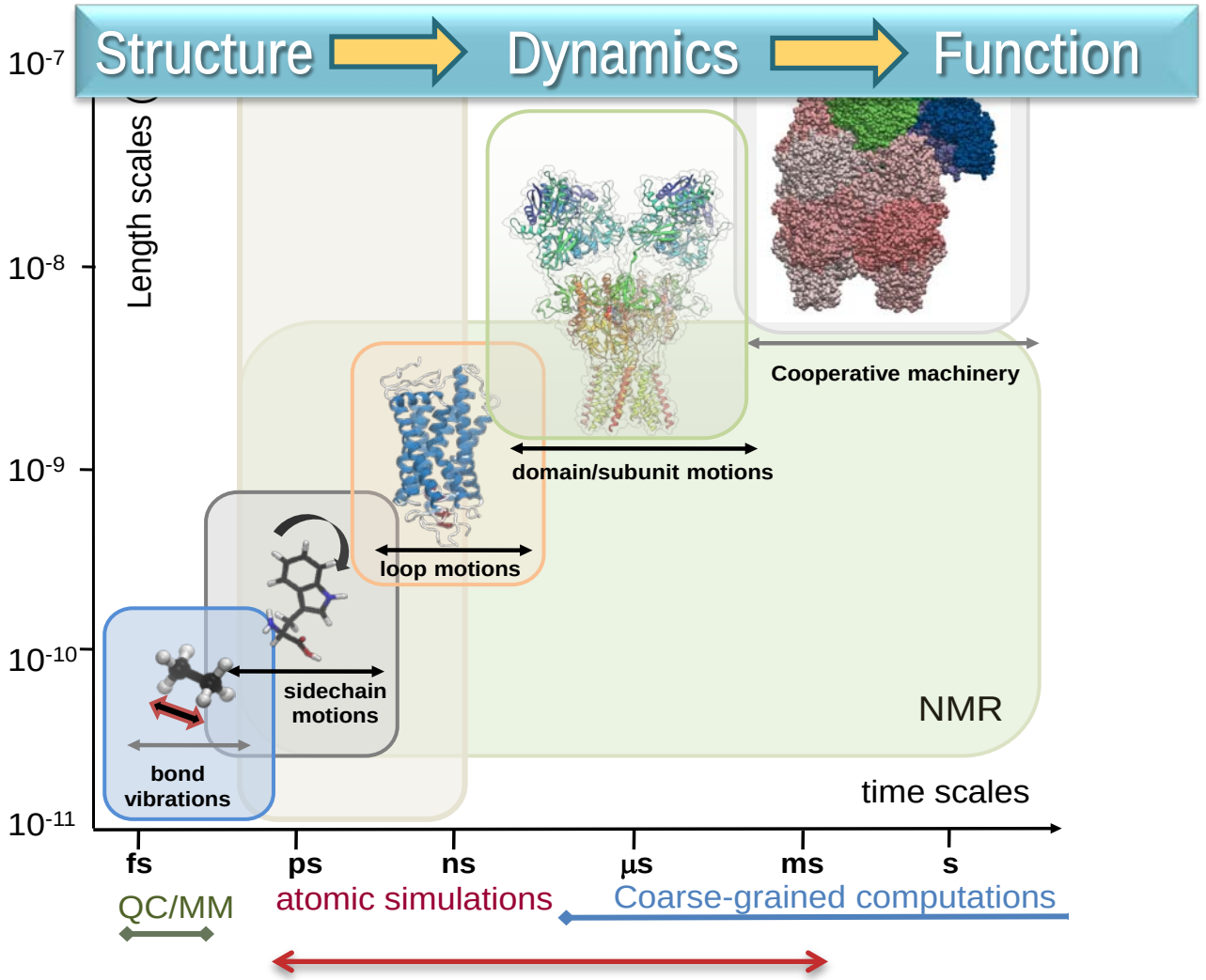
from 6 x 6 x 5 μm^3 sample of adult rat hippocampal stratum radiatum neuropil

Goal: to generate data for mesoscopic scale

Developing integrated *methodology for complex systems dynamics, to enable information transfer across scales*



Each structure encodes a unique dynamics



Physics-based approach

- Statistical Mechanics of Polymers
- Theory of Rubber Elasticity

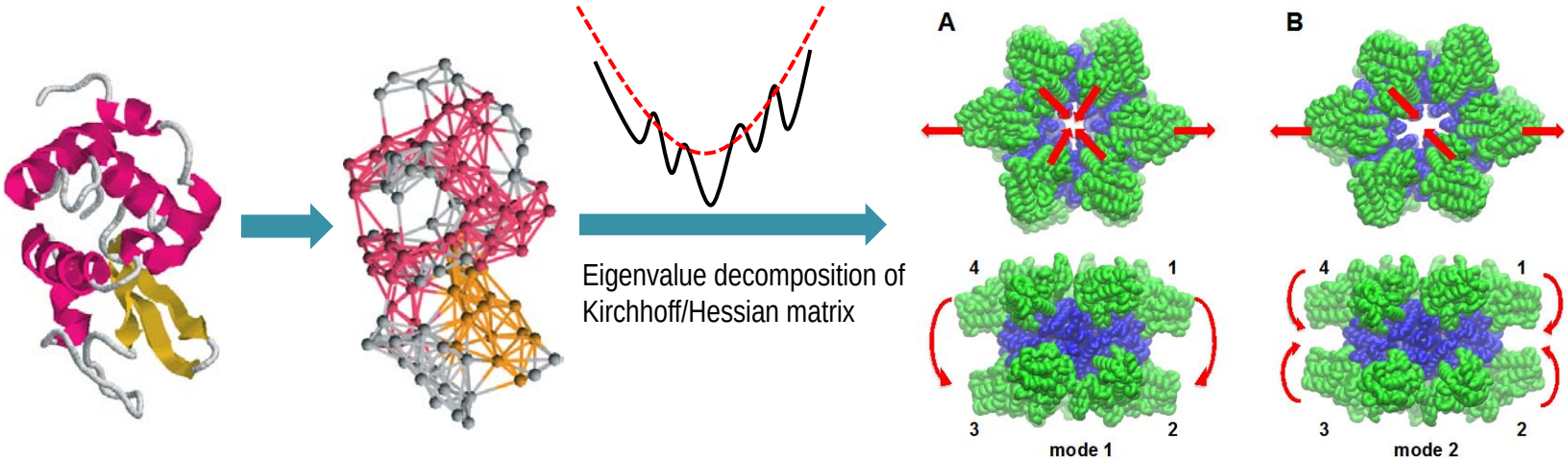
Paul J. Flory (1910-1985)
Nobel Prize in Chemistry 1974

Elastic Network Model for Proteins

And Pearson (1976), Eichinger (1980), Klockzkowski, Erman & Mark (1989)…

Collective motions

using elastic network models (ENM)



GNM: Bahar et al *Fold & Des* 1996; Haliloglu et al. *Phys Rev Lett*1997
ANM: Doruker et al. *Proteins* 2000; Atilgan et al, *Biophys J* 2001

Based on theory of elasticity for polymer networks by **Flory, 1976**

Two elastic network models:

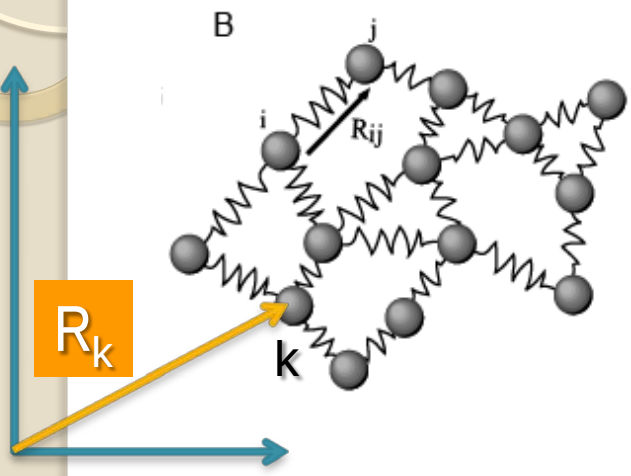
Gaussian Network Model (GNM)

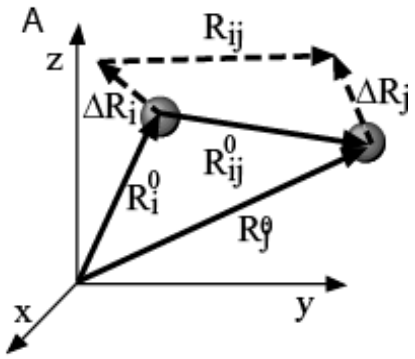
- Li H, Chang YY, Yang LW, Bahar I (2016) iGNM 2.0: the Gaussian network model database for bimolecular structural dynamics *Nucleic Acids Res* **44**: D415-422
- Bahar I, Atilgan AR, Erman B (1997) Direct evaluation of thermal fluctuations in protein *Folding & Design* **2**: 173-181.

Anisotropic Network Model (ANM)

- Eyal E, Lum G, Bahar I (2015) The Anisotropic Network Model web server at 2015 (ANM 2.0)*Bioinformatics* **31**: 1487-9
- Atilgan AR, Durrell SR, Jernigan RL, Demirel MC, Keskin O, Bahar I (2001) Anisotropy of fluctuation dynamics of proteins with an elastic network model *Biophys J* **80**: 505-515.

Gaussian Network Model (GNM)





- Each node represents a residue
- Residue positions, **R**i, identified by α-carbons' coordinates
- Springs connect residues located within a cutoff distance (e.g., 10 Å)

→ Nodes are subject to **Gaussian fluctuations** ΔR_i

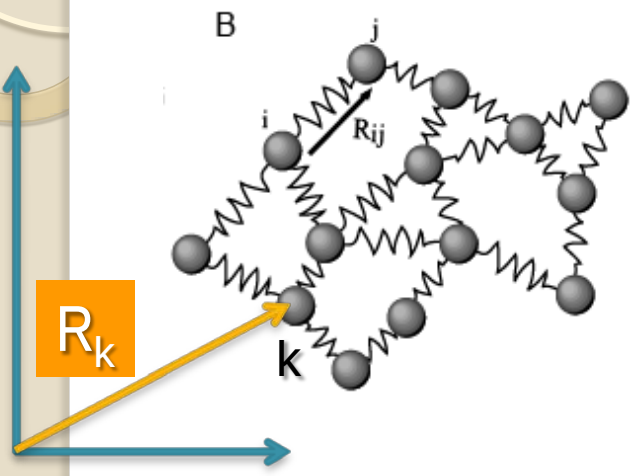
→ Inter-residue distances R_{ij} also undergo Gaussian fluctuations

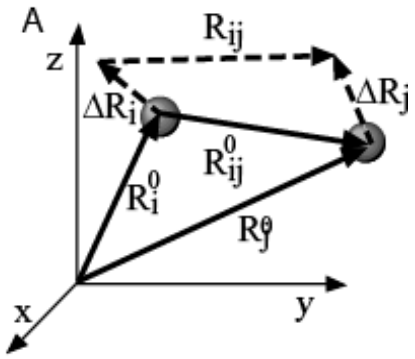
→ $\Delta \mathbf{R}_{ij} = \Delta \mathbf{R}_j - \Delta \mathbf{R}_i$

Fluctuations in residue positions

Bahar, Atilgan & Erman, *Fold & Des* 1997

Gaussian Network Model (GNM)





Fluctuation vector:

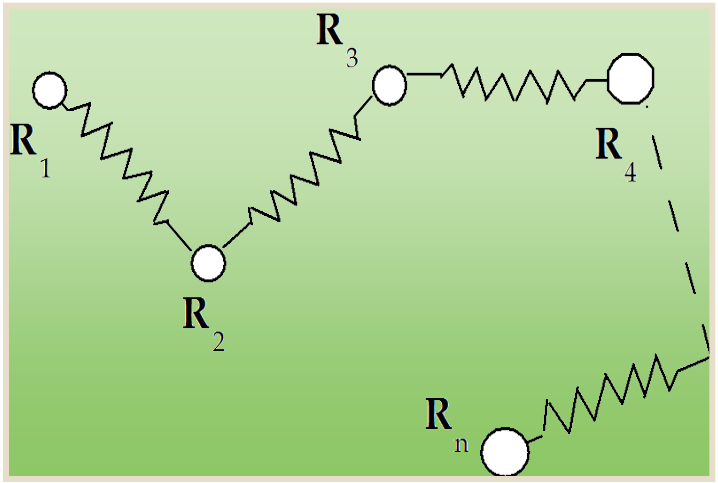
$$\rightarrow \Delta \mathbf{R} = \begin{bmatrix} \Delta \mathbf{R}_1 \\ \Delta \mathbf{R}_2 \\ \Delta \mathbf{R}_3 \\ \Delta \mathbf{R}_4 \\ .. \\ .. \\ .. \\ .. \\ \Delta \mathbf{R}_N \end{bmatrix}$$

Fluctuations in residue positions

Bahar, Atilgan & Erman, *Fold & Des* 1997

Rouse model for polymers

Classical bead-and-spring model



Kirchhoff matrix

$$\Gamma = \begin{bmatrix} 1 & -1 & & & & & \\ -1 & 2 & -1 & & & & \\ & -1 & 2 & -1 & & & \\ & & & .. & ... & & \\ & & & & -1 & 2 & -1 \\ & & & & & -1 & 1 \end{bmatrix}$$

$\Delta \mathbf{R}_{12} = \mathbf{R}_{12} - \mathbf{R}_{12}^{0}$

Force constant

$$V_{tot} = (\gamma/2) [(\Delta R_{12})^2 + (\Delta R_{23})^2 + ... (\Delta R_{N-1,N})^2]$$

$$= (\gamma/2) [(\Delta R_2 - \Delta R_1)^2 + (\Delta R_3 - \Delta R_2)^2 + ... $$

Rouse model for polymers

Kirchhoff matrix

$$\Gamma = \begin{bmatrix} 1 & -1 & & & & & \\ -1 & 2 & -1 & & & & \\ & -1 & 2 & -1 & & & \\ & & & .. & ... & & \\ & & & & -1 & 2 & -1 \\ & & & & & -1 & 1 \end{bmatrix}$$

Force constant

$$V_{tot} = (\gamma/2) [(\Delta R_{12})^2 + (\Delta R_{23})^2 + ... (\Delta R_{N-1,N})^2]$$

$$= (\gamma/2) [(\Delta R_2 - \Delta R_1)^2 + (\Delta R_3 - \Delta R_2)^2 + ...$$

Rouse model for polymers

Fluctuation vector

$(\gamma/2)\ [\Delta R_1\ \ \Delta R_2\ \ \Delta R_3\ \ldots.\ \ \Delta R_N]$

Kirchhoff matrix

$$\begin{bmatrix} 1 & -1 & & & & & \\ -1 & 2 & -1 & & & & \\ & -1 & 2 & -1 & & & \\ & & & .. & ... & & \\ & & & & -1 & 2 & -1 \end{bmatrix} \begin{bmatrix} \Delta R_1 \\ \Delta R_2 \\ \Delta R_3 \end{bmatrix} =$$

$$V_{tot} = (\gamma/2)\ \Delta R^T\ \Gamma\ \Delta R$$

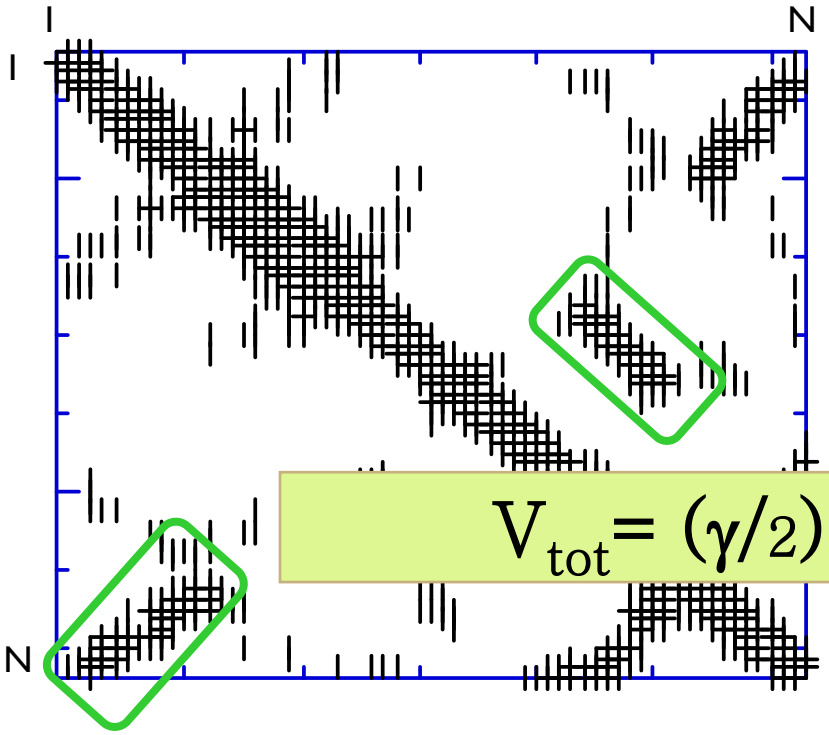
Force constant

$$V_{tot} = (\gamma/2)\ [\ (\Delta R_{12})^2 + (\Delta R_{23})^2 + \ldots\ldots\ (\Delta R_{N-1,N})^2\ ]$$

$$= (\gamma/2)\ [\ (\Delta R_2 - \Delta R_1)^2 + (\Delta R_3 - \Delta R_2)^2 + \ldots\ldots$$

Kirchhoff matrix for inter-residue contacts

For a protein of N residues

$\Gamma =$ 

$$\Gamma_{ik} = \begin{cases} -1 & \text{if } r_{ik} < r_{cut} \\ 0 & \text{if } r_{ik} > r_{cut} \end{cases}$$

$$\Gamma_{ii} = -\sum_k \Gamma_{ik}$$

$$V_{tot} = (\gamma/2)\, \Delta R^T \Gamma \Delta R$$

Γ provides a complete description of contact topology!

Statistical mechanical averages

For a protein of N residues

$$< \Delta \boldsymbol{R}_i \bullet \Delta \boldsymbol{R}_j > \; = (1/Z_N) \int (\Delta \boldsymbol{R}_i \bullet \Delta \boldsymbol{R}_j)\, e^{-V/k_B T} d\{\Delta \boldsymbol{R}\}$$

$$= (3 k_B T / \gamma) \left[\boldsymbol{\Gamma}^{-1}\right]_{ij}$$

$\boldsymbol{\Gamma}$ provides a complete description of contact topology!

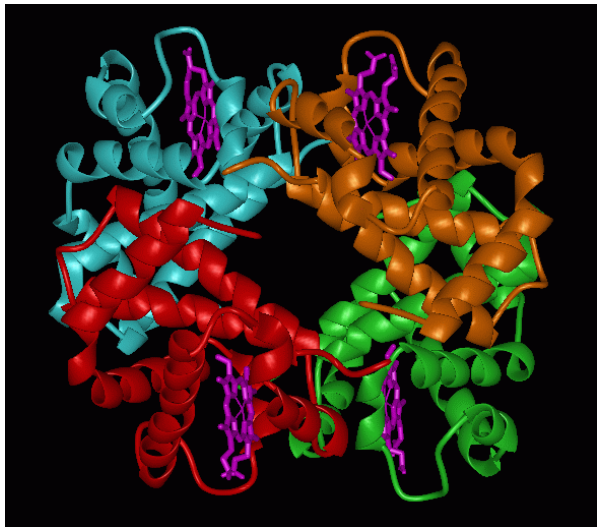
Kirchhoff matrix determines the mean-square fluctuations

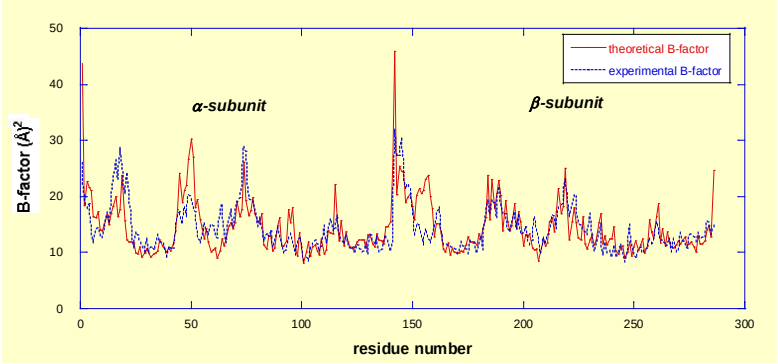
$$[\mathbf{\Gamma}^{-1}]_{ii} \sim \langle(\Delta \mathbf{R}_i)^2\rangle$$

And cross-correlations between residue motions

$$[\mathbf{\Gamma}^{-1}]_{ij} \sim \langle(\Delta \mathbf{R}_i \,.\, \Delta \mathbf{R}_j)\rangle$$

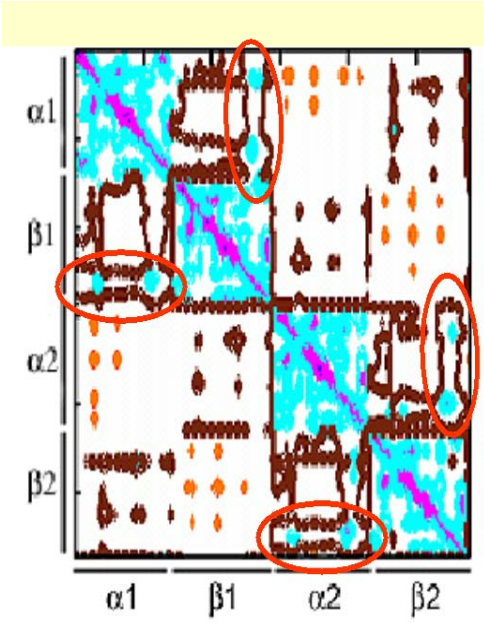
1. Application to hemoglobin





B- factors – Comparison with experiments

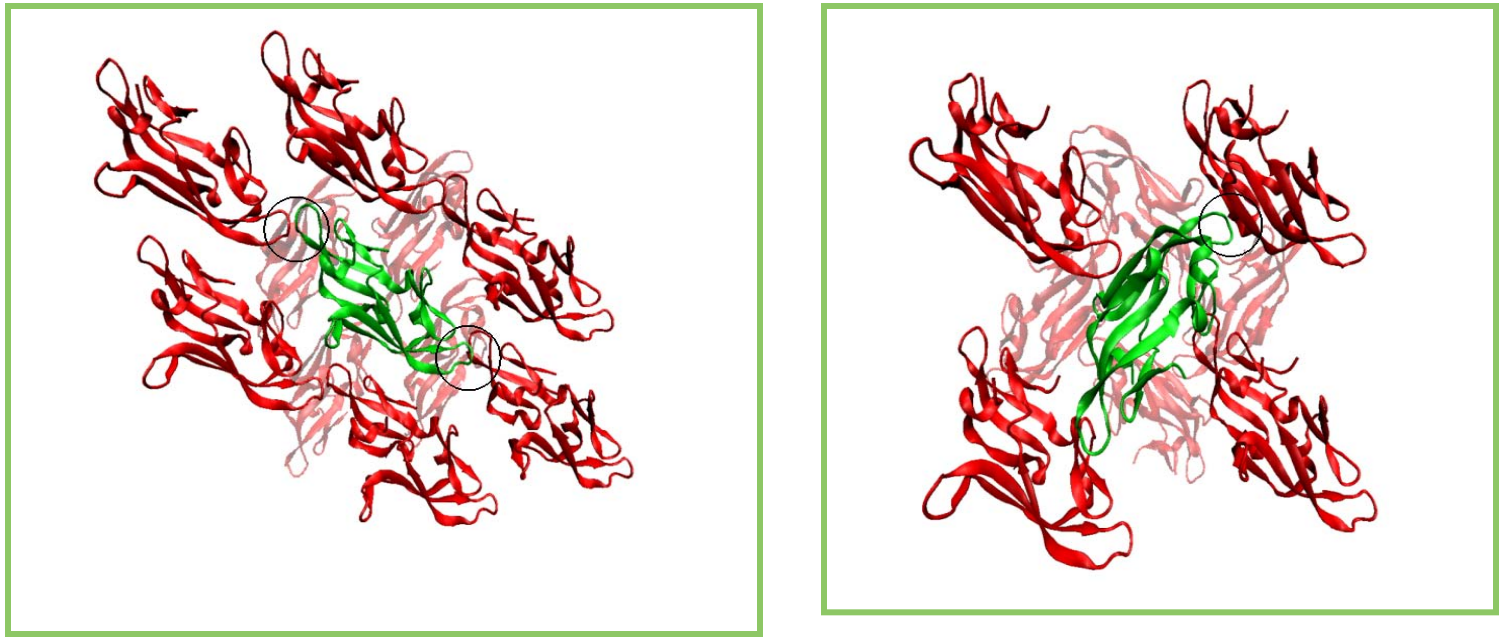
$$B_i = 8\pi^2/3 \langle(\Delta R_i)^2\rangle$$



Intradimer cooperativity – Symmetry rule (Yuan et al. JMB 2002; Ackers et al. PNAS 2002.)

C. Xu, D. Tobi and I. Bahar (2003) *J. Mol. Biol.* 2003, 153-168

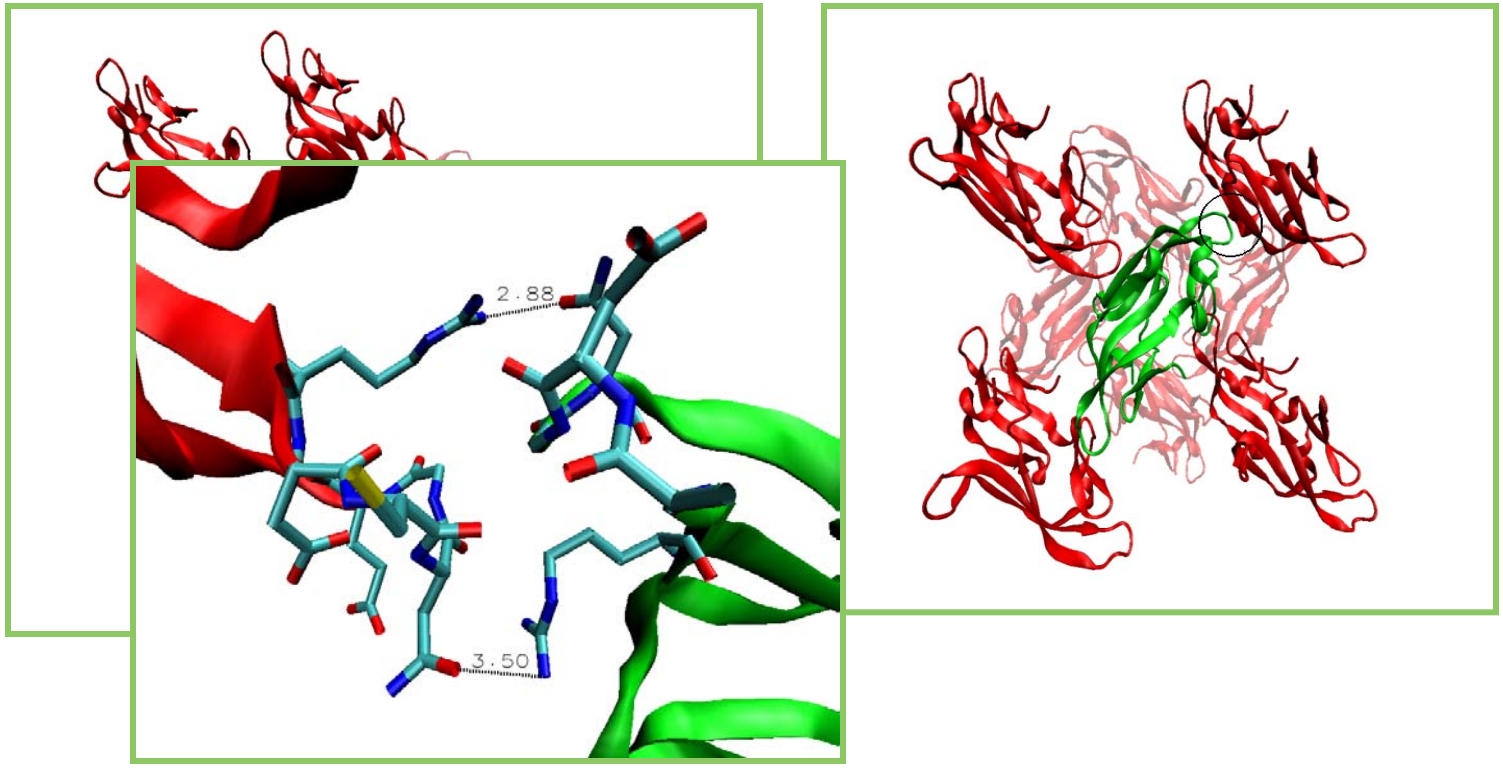
B-factors are affected by crystal contacts



Two X-ray structures for a designed sugar-binding protein LKAMG

1

B-factors are affected by crystal contacts



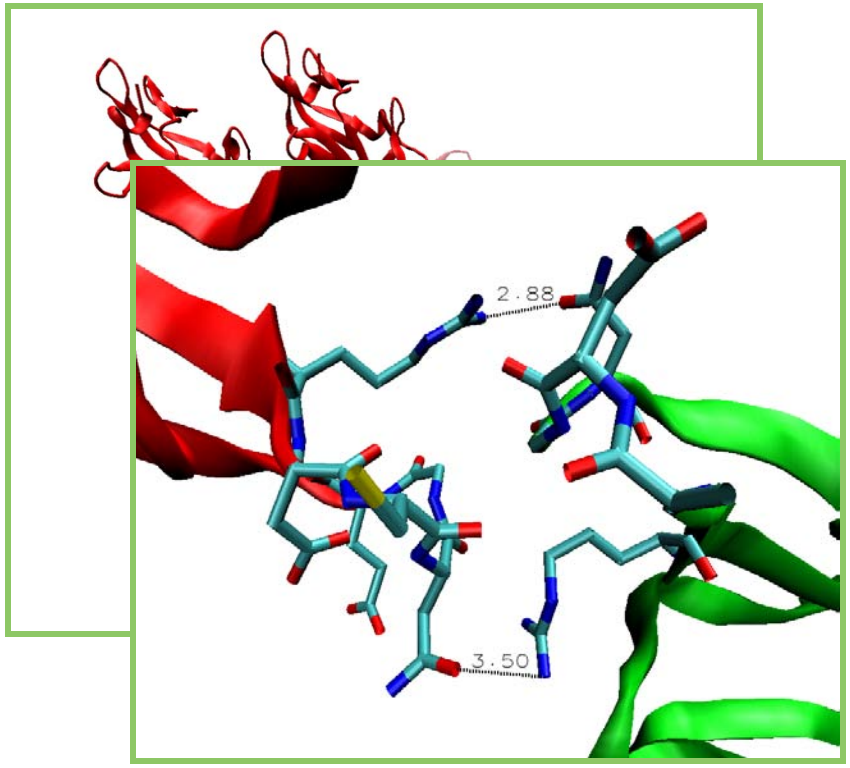
Particular loop motions are curtailed by intermolecular contacts in the crystal environment causing a discrepancy between theory and experiments

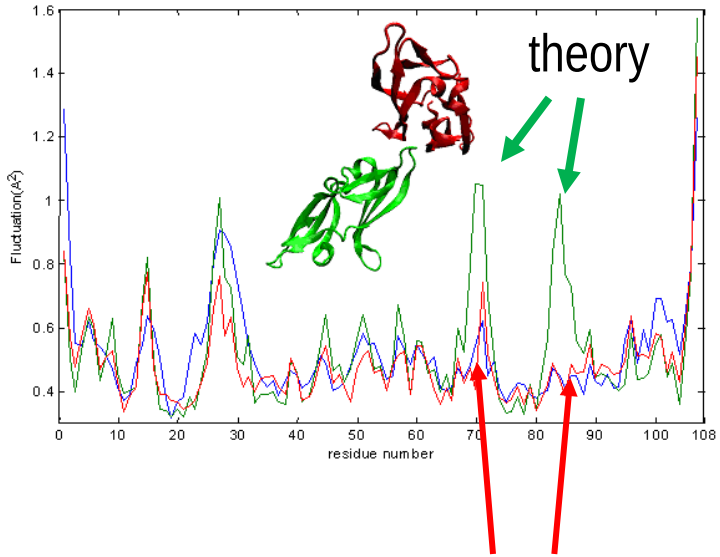
FOR MORE INFO...

Liu, Koharudin, Gronenborn & Bahar (2009) *Proteins 77, 927-939.*

1

Agreement between theory and experiments upon inclusion of crystal lattice effects into the GNM





Crystal contacts

Particular loop motions are curtailed by intermolecular contacts in the crystal environment causing a discrepancy between theory and experiments

FOR MORE INFO...

Liu, Koharudin, Gronenborn & Bahar (2009) *Proteins 77, 927-939.*

Collective Motions Encoded by the Structure: Normal Modes

Several modes contribute to dynamics

$$< \Delta \mathbf{R}_i \bullet \Delta \mathbf{R}_j > = \sum_k [\Delta \mathbf{R}_i \bullet \Delta \mathbf{R}_j]_k$$

Contribution of mode k

$$< \Delta \mathbf{R}_i \bullet \Delta \mathbf{R}_j > = (3k_B T / \gamma) \left[\mathbf{\Gamma}^{-1} \right]_{ij}$$

Contribution of mode k

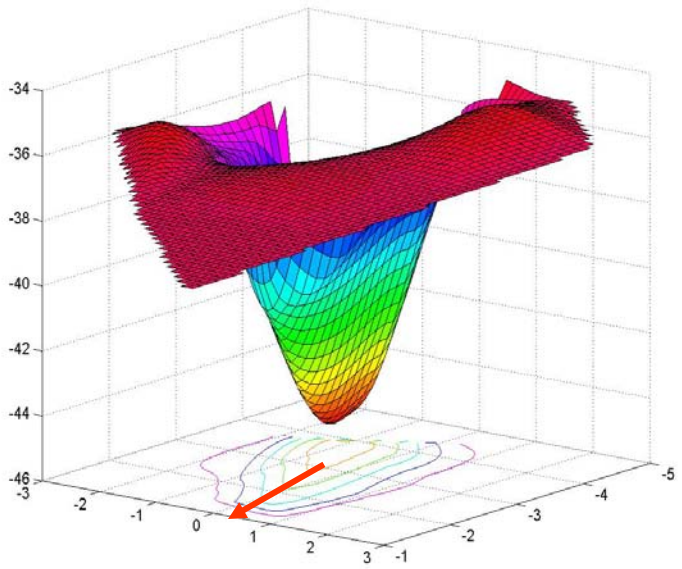
$$[\Delta \mathbf{R}_i \bullet \Delta \mathbf{R}_j]_k = (3k_B T / \gamma) \left[\lambda_k^{-1} \mathbf{u}_k \mathbf{u}_k^T \right]_{ij}$$

expressed in terms of kth eigenvalue λ_k and kth eigenvector $\mathbf{u}_k$ of $\mathbf{\Gamma}$

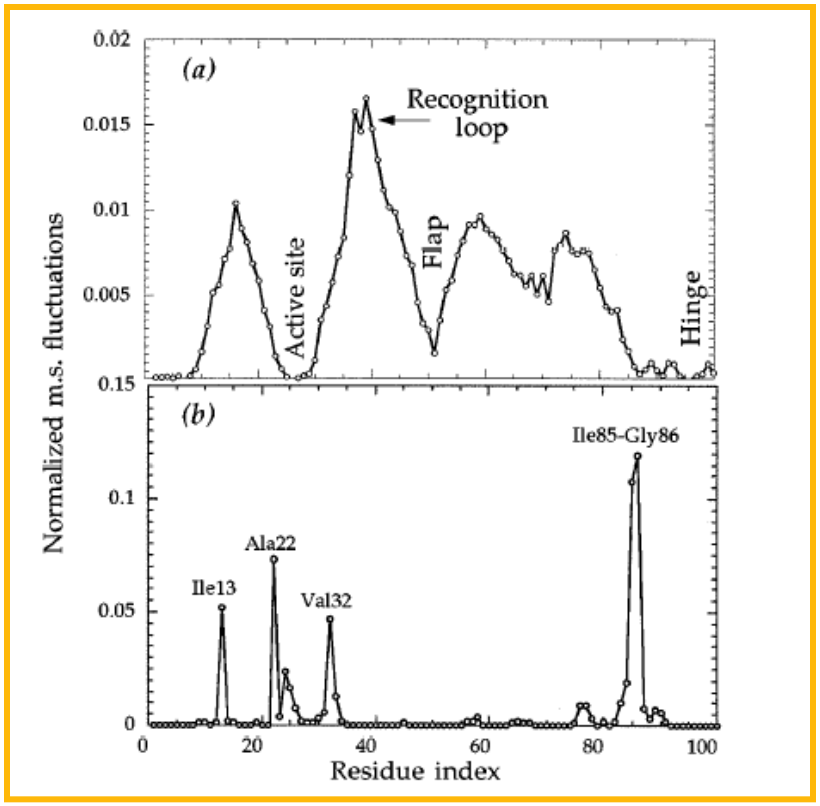
FOR MORE INFO...

Bahar et al. (1998) Phys Rev Lett. 80, 2733

Several modes contribute to dynamics



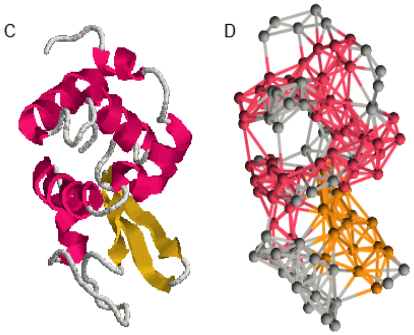
The first mode selects
the 'easiest' collective motion



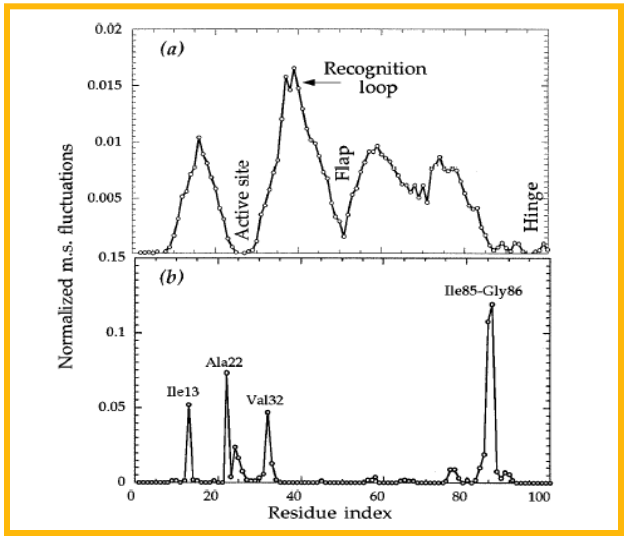
FOR MORE INFO...

Bahar et al. (1998) Phys Rev Lett. 80, 2733

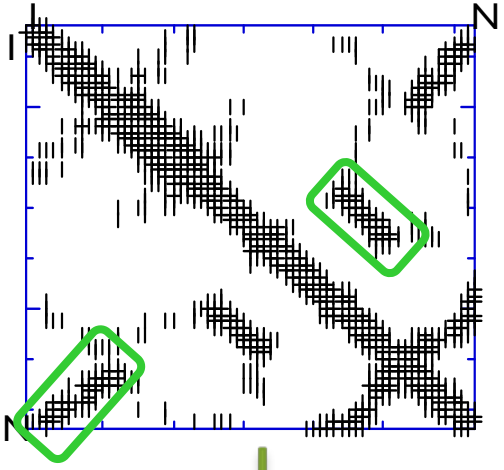
Summary - Gaussian network model (GNM)



$$[\Delta \mathbf{R}_i \bullet \Delta \mathbf{R}_i]_k = (3k_B T/\gamma)\left[\lambda_k^{-1}\mathbf{u}_k\mathbf{u}_k^T\right]_{ii}$$



Kirchhoff matrix for inter-residue contacts



Contact: $R_{ij} < 10\text{Å}$

$\Gamma =$

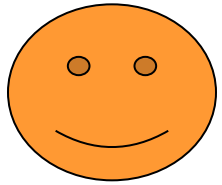
Several modes of motion contribute to dynamics

MSF of residue *i* = $<(\Delta R_i)^2>$

$$<(\Delta R_i)^2> = (3\,k_B\,T/\gamma)\left[\Gamma^{-1}\right]_{ii}$$

Recipe (GNM)

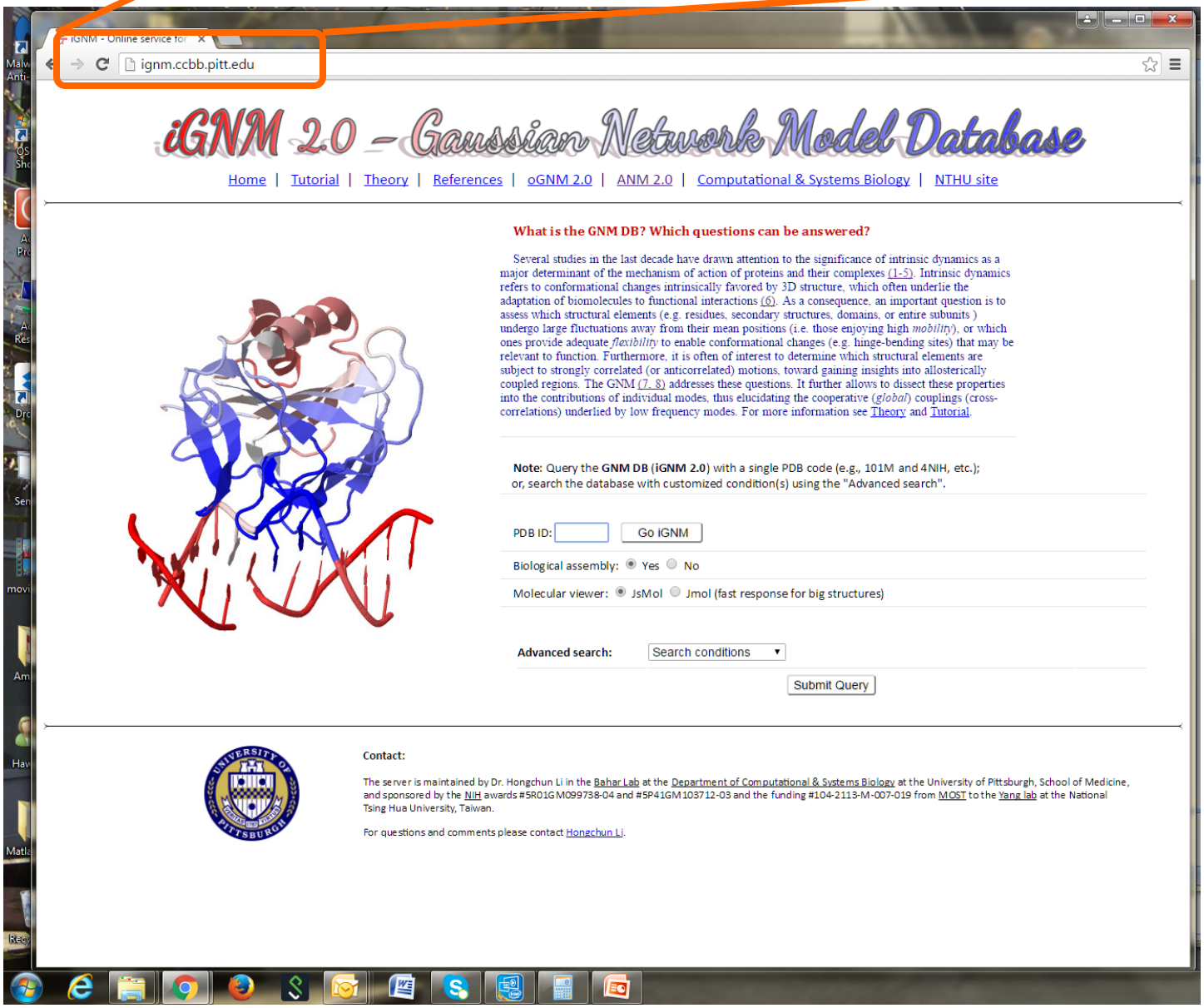
- Construct the network of masses and springs
- Write the corresponding Kirchhoff matrix G
- Eigenvalue decomposition of G yields
  the eigenvalues $\lambda_1, \lambda_2, \lambda_3, \ldots\ldots, \lambda_{N-1}$ (and $\lambda_0 = 0$)
  and eigenvectors $u_1, u_2, u_3, \ldots\ldots u_{N-1}$ (and u_0)



Properties

- the eigenvalues scale with the frequency squared ($\lambda_i \sim w_i^2$)
- eigenvectors are N-dim vectors, eigenvalues are scalars
- the i^{th} element of u_k represents the displacement of node *i* in mode *k*
- the eigenvectors are normalized, i.e. $u_k \bullet u_k = 1$ for all *k*
- as such, the squared elements of u_k represent the 'mobility' distribution
- dynamics results from the superposition of all modes
- $\lambda_k^{-1/2}$ serves as the weight of u_k → low frequency modes have high weights

ignm.ccbb.pitt.edu



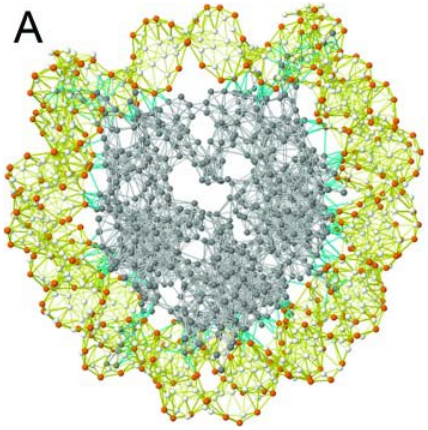
Why use iGNM2.0?

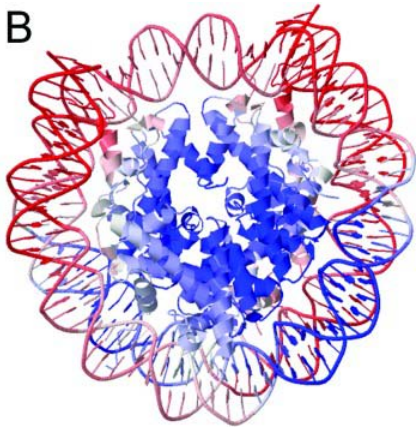
- Easy access to precomputed results for 95% of the PDB including
  - the largest structures beyond the scope of MD
  - protein-DNA/RNA complexes
  - biological assemblies (intact, biologically functional structures)

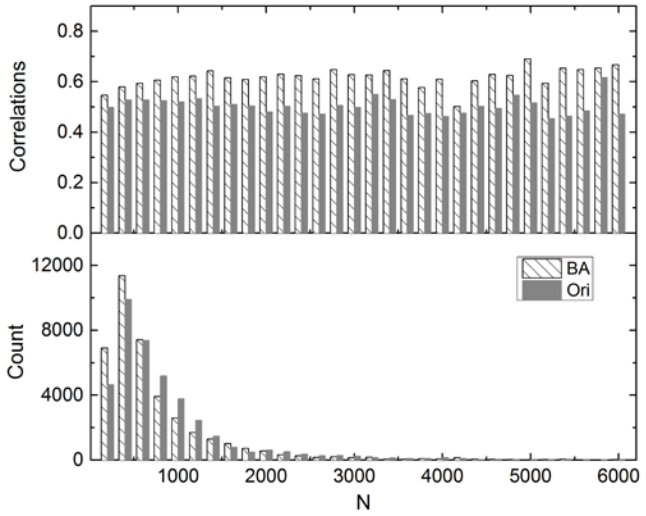
- Easy to understand, visualize, make functional inferences for any structure

13.9% of the structures in the *i*GNM 2.0 (14,899 out of 107,201) contain >10^3 nodes

The biological assembly of 39,505 PDB structures is different from the default structure reported in the PDBs (as asymmetric unit)







Collective motions are functional

Collectivity (2D) for a given mode *k* is a measure of the degree of cooperativity (between residues) in that mode, defined as (*)

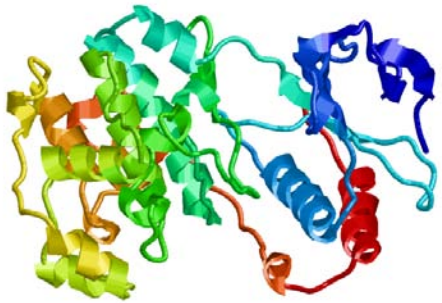
$$Collectivity_k = \frac{1}{N} e^{-\sum_i^N u_{k,i}^2 \ln u_{k,i}^2}$$

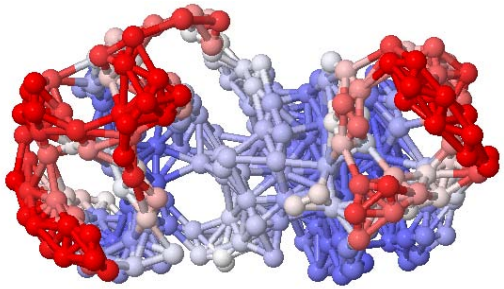
Information entropy associated with residue fluctuations in mode k

where, *k* is the mode number and *i* is the residue index. A larger collectivity value refers to a more distributive mode and *vice versa*. Usually soft modes are highly collective.

(*) Brüschweiler R. Collective protein dynamics and nuclear spin relaxation. J. Chem. Phys. 1995;102:3396–340

Anisotropic Network Model (ANM)

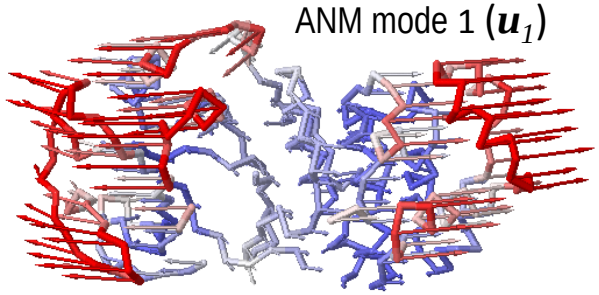




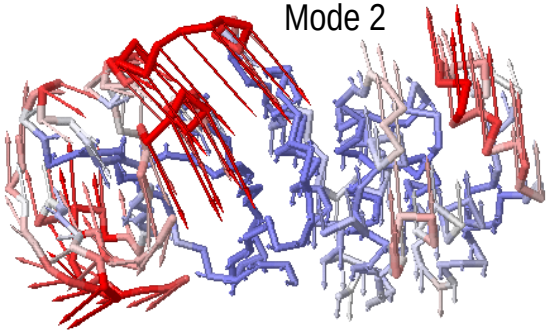
$$\mathbf{H} = \sum_{i=1}^{3N-6} \lambda_i \; \boldsymbol{u}_i \boldsymbol{u}_i^{\mathbf{T}}$$

$$\mathbf{H}^{(ij)} = \frac{\gamma \, \mathbf{\Gamma}_{ij}}{\left(R_{ij}^0\right)^2} \begin{bmatrix} X_{ij}X_{ij} & X_{ij}Y_{ij} & X_{ij}Z_{ij} \\ Y_{ij}X_{ij} & Y_{ij}Y_{ij} & Y_{ij}Z_{ij} \\ Z_{ij}X_{ij} & Z_{ij}Y_{ij} & Z_{ij}Z_{ij} \end{bmatrix}$$

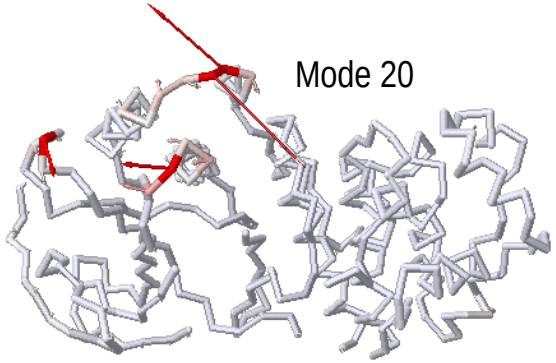
ANM mode 1 ($\boldsymbol{u}_1$)

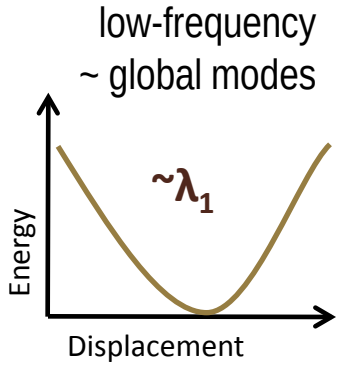


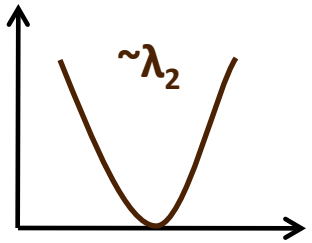
Mode 2



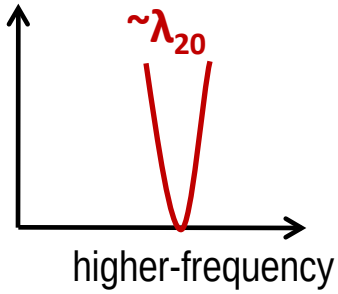
Mode 20







$\lambda_1 < \lambda_2 < \lambda_3 < \ldots$



Doruker et al. (2000) *Proteins*; Atilgan AR et al. (2001) *Biophys J.*; Eyal et al. (2006) *Bioinformatics* 22, 2619

Anisotropic Network Model

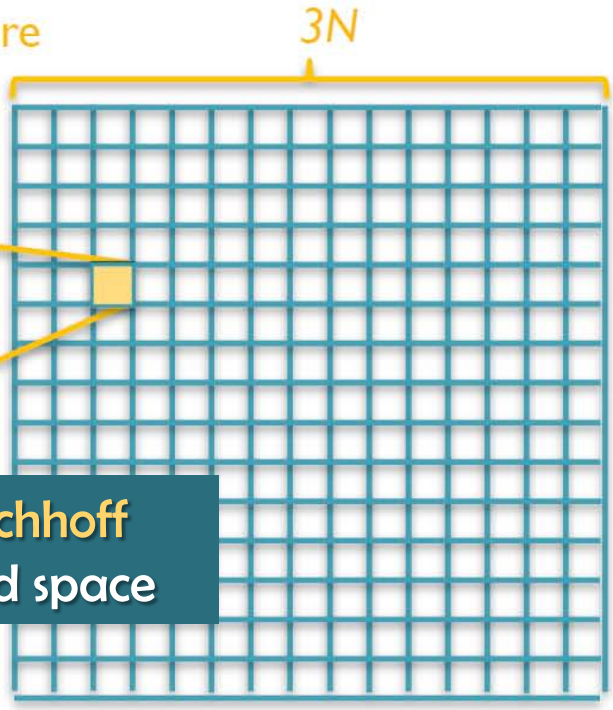
$$V(\mathbf{r}) = \frac{\gamma}{2}\sum_{i=1}^{N}\sum_{j>i}\left(|\mathbf{r}_{ij}| - |\mathbf{r}_{ij}^0|\right)^2 \Theta\left(R_c - |\mathbf{r}_{ij}^0|\right)$$

Harmonic Step function

$$\left(\frac{\partial^2 V}{\partial x_i \partial y_j}\right)_{\mathbf{r}^0} = -\frac{x_i^0 y_j^0}{|\mathbf{r}_{ij}^0|^2}$$

Hessian is calculated directly from structure

$$\mathbf{H_{ij}} = -\frac{\gamma}{(R_{ij}^0)^2}\begin{bmatrix} (x_{ij}^0)^2 & x_{ij}^0 y_{ij}^0 & x_{ij}^0 z_{ij}^0 \\ x_{ij}^0 y_{ij}^0 & (y_{ij}^0)^2 & y_{ij}^0 z_{ij}^0 \\ x_{ij}^0 z_{ij}^0 & y_{ij}^0 z_{ij}^0 & (z_{ij}^0)^2 \end{bmatrix}$$

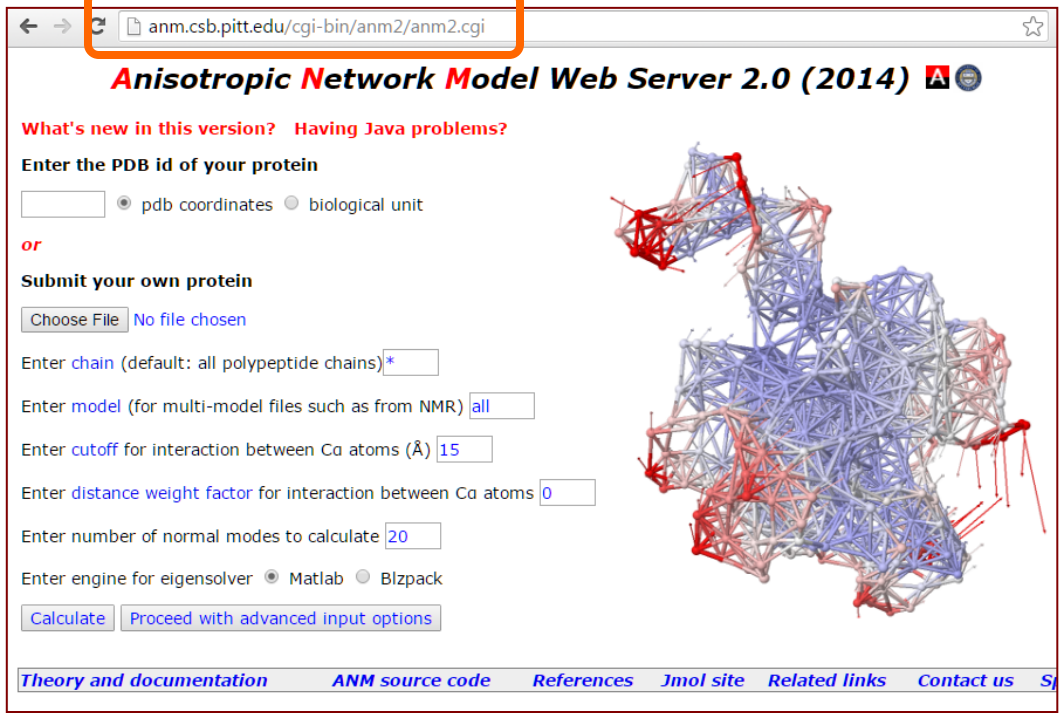


3N x 3N Hessian of ANM replaces the NxN Kirchhoff matrix of GNM – to yield mode shapes in 3N-d space

Doruker et al. Proteins 40 (2000).
Atilgan et al. Biophys J 80 (2001).

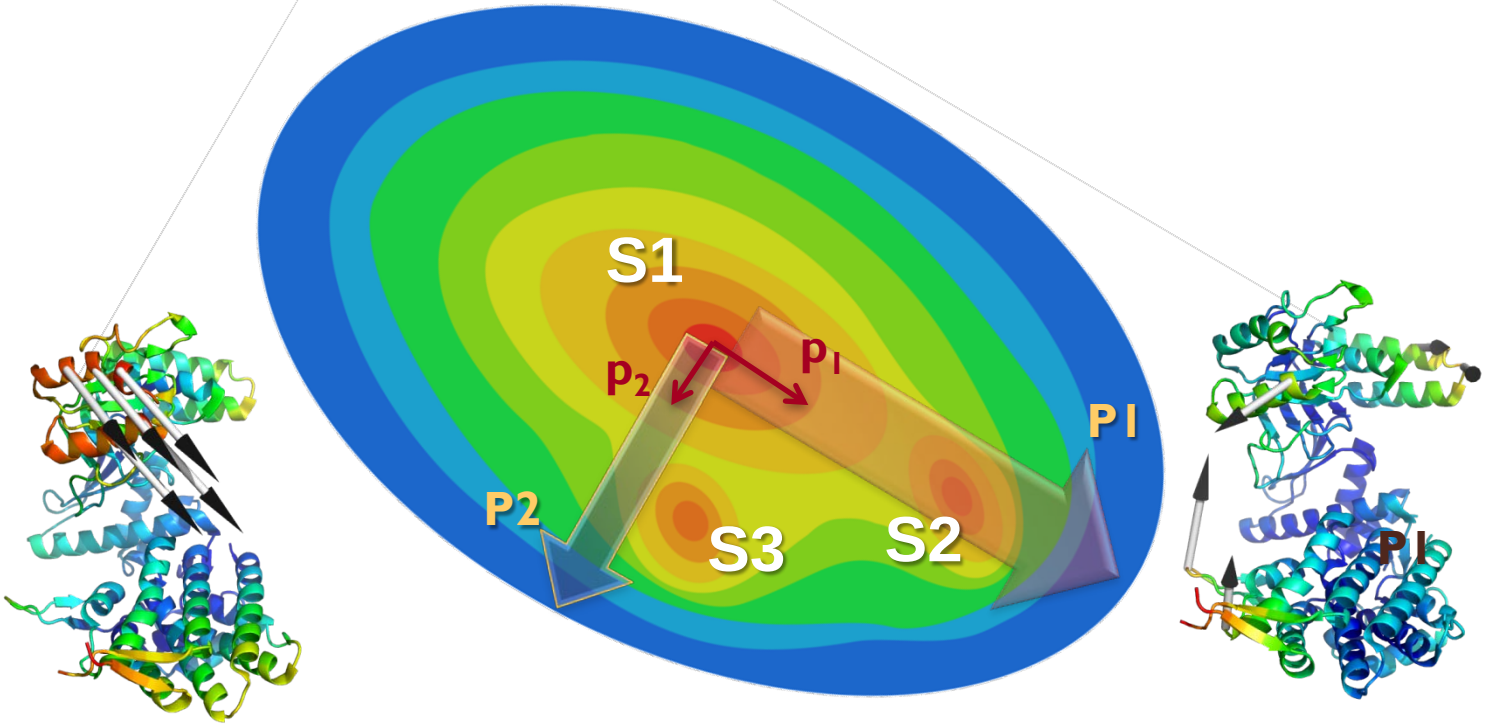
ANM server

http://anm.csb.pitt.edu/cgi-bin/anm2/anm2.cgi



2

Substates may be identified along soft modes

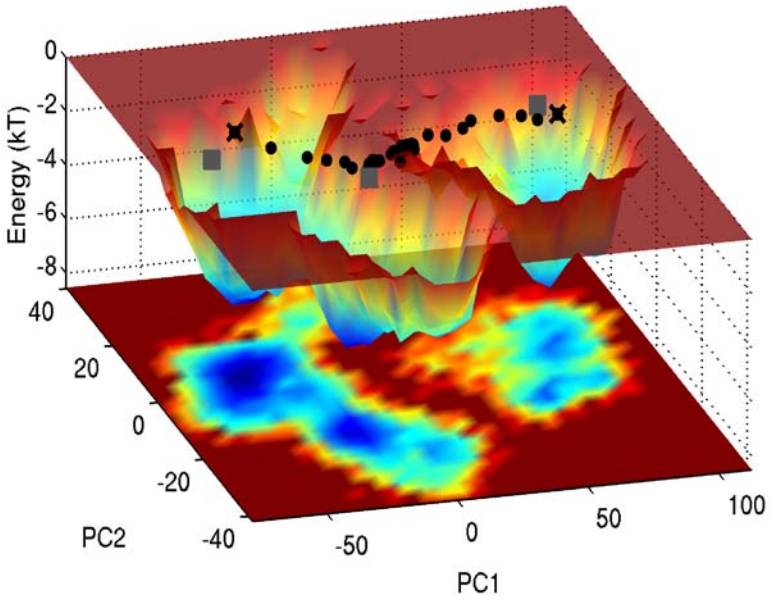


Hybrid ANM/MD methods include atomic details and specificity

2

Co-MD: Guiding MD simulations by ANM modes

Dr. Mert Gur



ANM-guided transition pathways

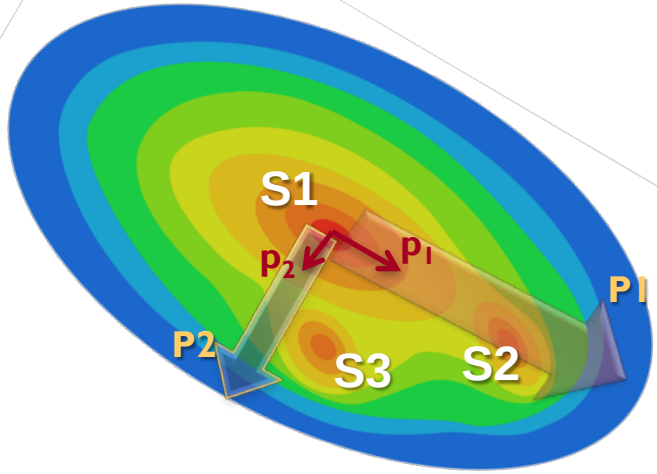
- Isin B, Schulten K, Tajkhorshid E, Bahar I (2008) *Biophysical J* 95: 789-803.
- Yang Z, Májek P, Bahar I (2009) *PLoS Comput Biol* 5: e1000360.
- Gur M, Madura JD, Bahar I (2013) *Biophys J* 105:1643-52
- Das A, Gur M, Cheng MH, Jo S, Bahar I, Roux B (2014) *PLoS Comput Biol* 10: e1003521

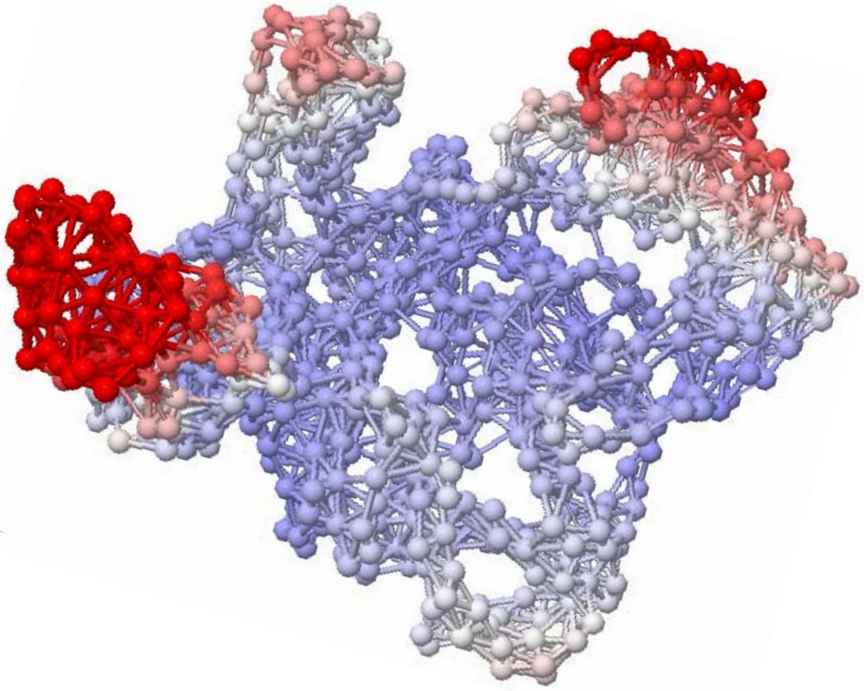
coMD trajectories proceed along the minima of free energy landscape

Allosteric changes in conformation

ANM (anisotropic network model)

Elastic Network Models are particularly useful for exploring the allosteric dynamics of large multimeric structures

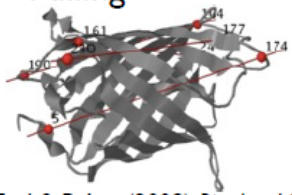




Comparison with experimental data shows that the functional movements are those predicted by the ENM to be intrinsically encoded by the structure

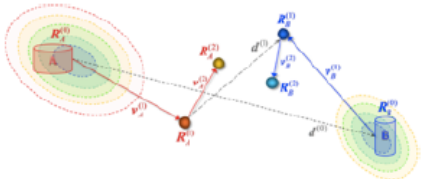
Other ENM applications

Pulling



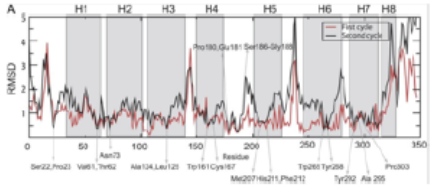
Eyal & Bahar (2008) *Biophys J* **94**:3424.

Transitions



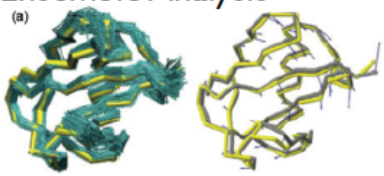
Z Yang et al. (2009) *PLoS Comput Biol* **5**:e1000360.

Steered MD



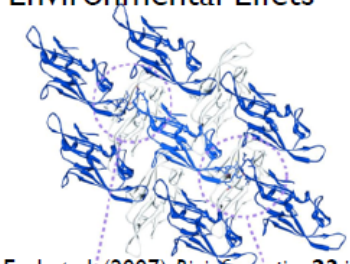
Isin et al. (2008) *Biophysical J* **95**:789.

Ensemble Analysis



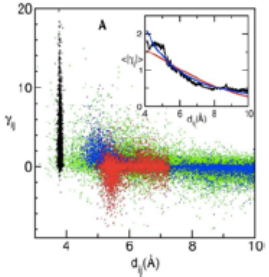
L-W Yang et al. (2009) *Bioinformatics* **25**: 606.
Bakan & Bahar (2009) *Proc Natl Acad Sci USA* **106**:14349.

Environmental Effets



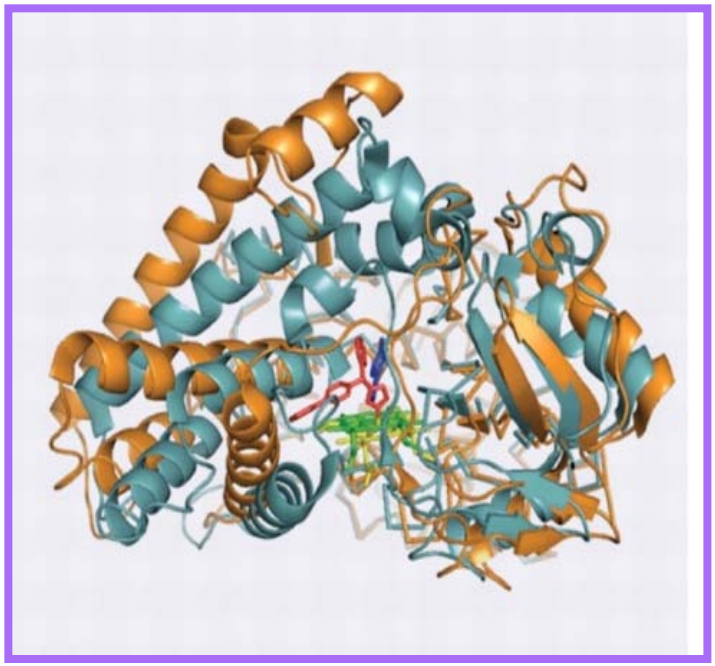
Eyal et al. (2007) *Bioinformatics* **23**:i175.
L Liu et al. (2009) *Proteins* **77**:927.

Model Optimization



Lezon & Bahar (2010) *PLoS Comput Biol* **6**:e1000816.

Intrinsically accessible motions enable
Optimal binding of substrate or drugs



Conformational flexibility + sequence variability mediates substrate selectivity

- Two conformations of P450-CYP2B4:

  open (orange) with a large substrate (bifonazole, red), and

  closed (light blue) with the smaller substrate 4-(4-chlorophenyl) imidazole (blue)

See...

N. Tokuriki and D. S. **Tawfik** (2009) *Science* **324**: 203-207

Session I: Plotting $<(\Delta R_i)^2>$ and contributions of selected modes

```
from prody import *
from pylab import *
anm = calcANM('1cot', selstr='calpha')
anm, cot = calcANM('1cot', selstr='calpha')
anm
cot
figure()
showProtein(cot)

figure()
showSqFlucts(anm)

figure()
showSqFlucts(anm[:10])

figure()
showSqFlucts(anm[:10], label='10 modes')
```

Application to cytochrome c
PDB: 1cot
A protein of 121 residues

cmd
ipython

Session 2: Viewing color-coded animations of individual modes

- writeNMD('cot_anm.nmd', anm, cot)

- *Start VMD*
- *select* Extensions → Analysis →Normal Mode Wizard
- *Select* 'Load NMD File'

Session 3: Cross-correlations $<(\Delta \mathbf{R}_i \cdot \Delta \mathbf{R}_j)>$ between fluctuations

- cross_corr = calcCrossCorr?
- cross_corr = calcCrossCorr(anm[0])
- figure()
- showCrossCorr(anm[0])
- writeHeatmap('anm_cross1.hm', cross_corr)

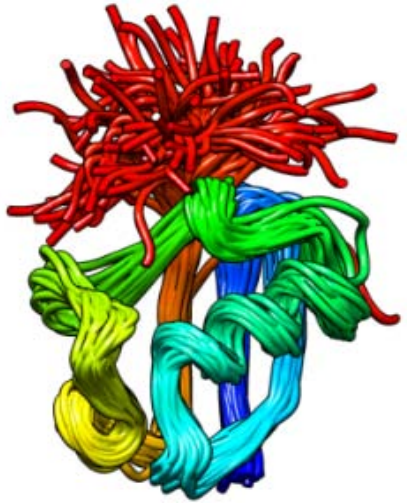
Session 4:
Viewing cross-correlations using VMD

- *VMD – Load file*
- *Select cot_anm.nmd (from your local folder)*
- *Load HeatMap*
- *open anm_cross1.hm (from your local folder)*

Ensembles of structures

- Structural changes accompanying substrate (protein) binding

- Structural changes induced by, or stabilized upon, ligand binding

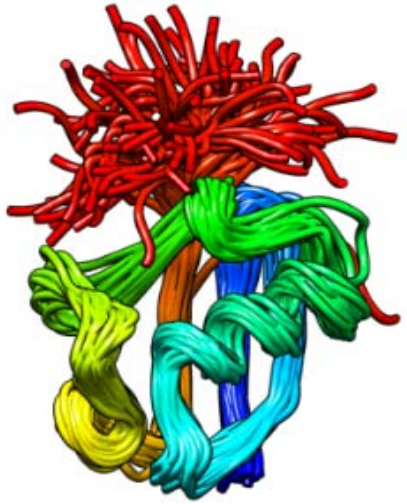


Ubiquitin
140 structures
1732 models

Ensembles of structures

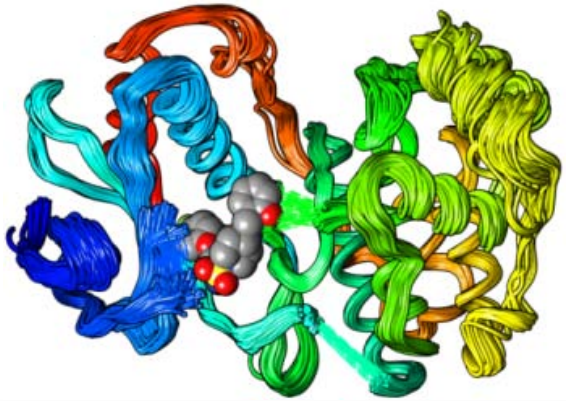
- Structural changes accompanying substrate (protein) binding

- Structural changes induced by, or stabilized upon, ligand binding

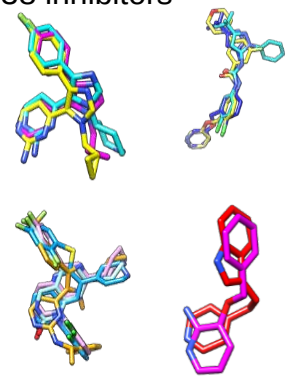


Ubiquitin
140 structures
1732 models

p38 MAP kinase
(**182 structures**)

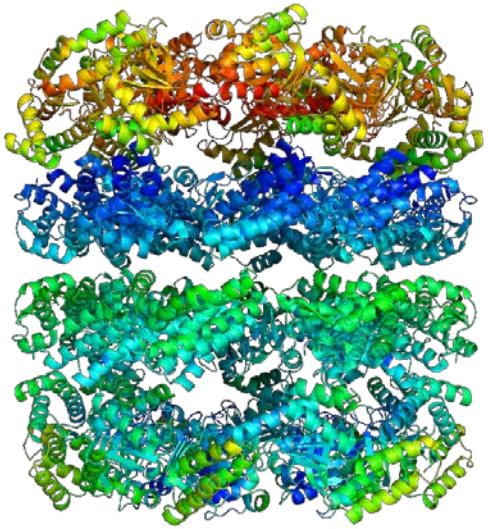


p38 inhibitors



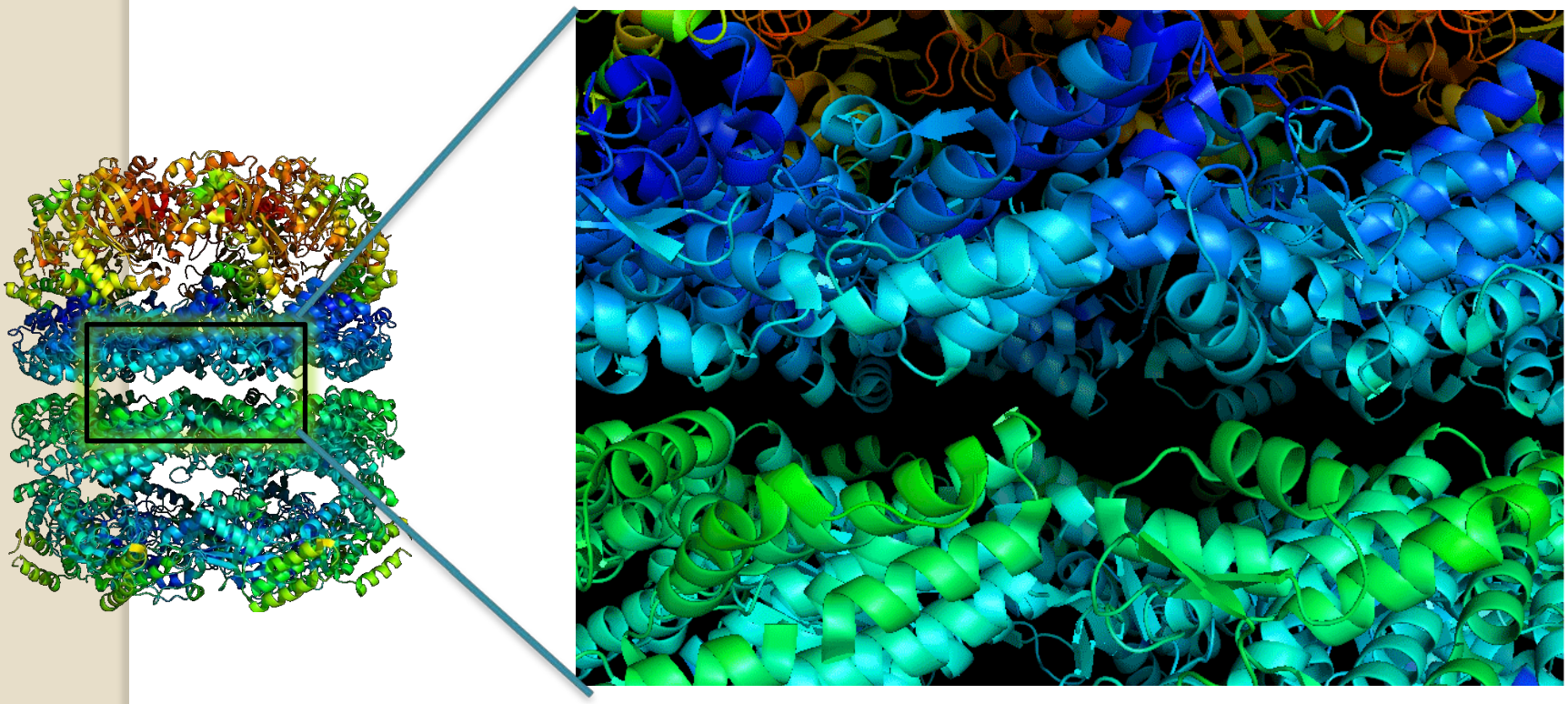
Ensembles of structures

- Structural changes accompanying substrate (protein) binding
- Structural changes induced by, or stabilized upon, ligand binding
- Alternative conformations sampled during allosteric cycles

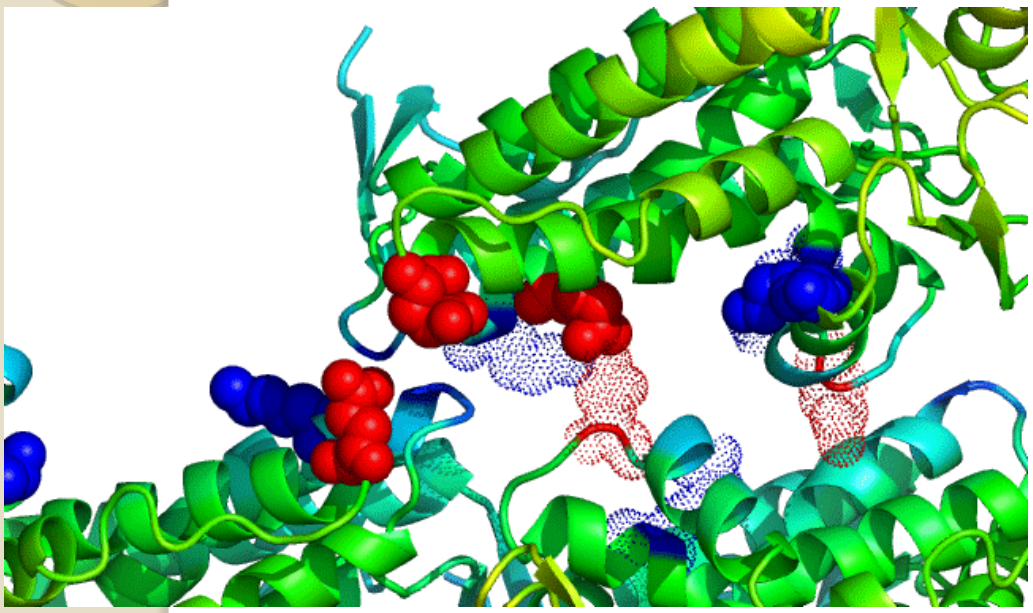


Yang et al. *PLoS Comp Biol* 2009

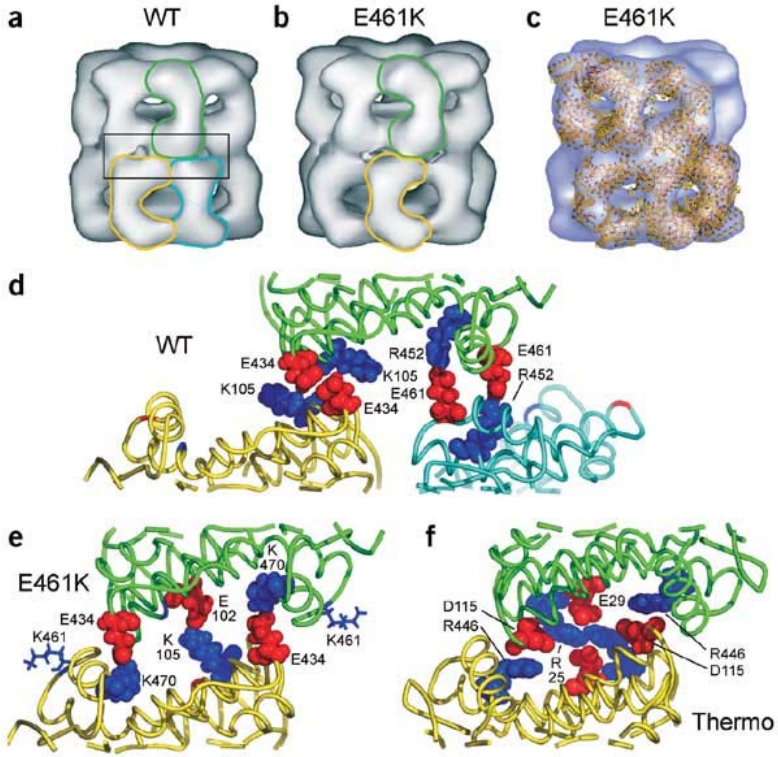
Redistribution of interactions at interfaces



Mutations may stabilizate conformers along soft modes – which may be dysfunctional



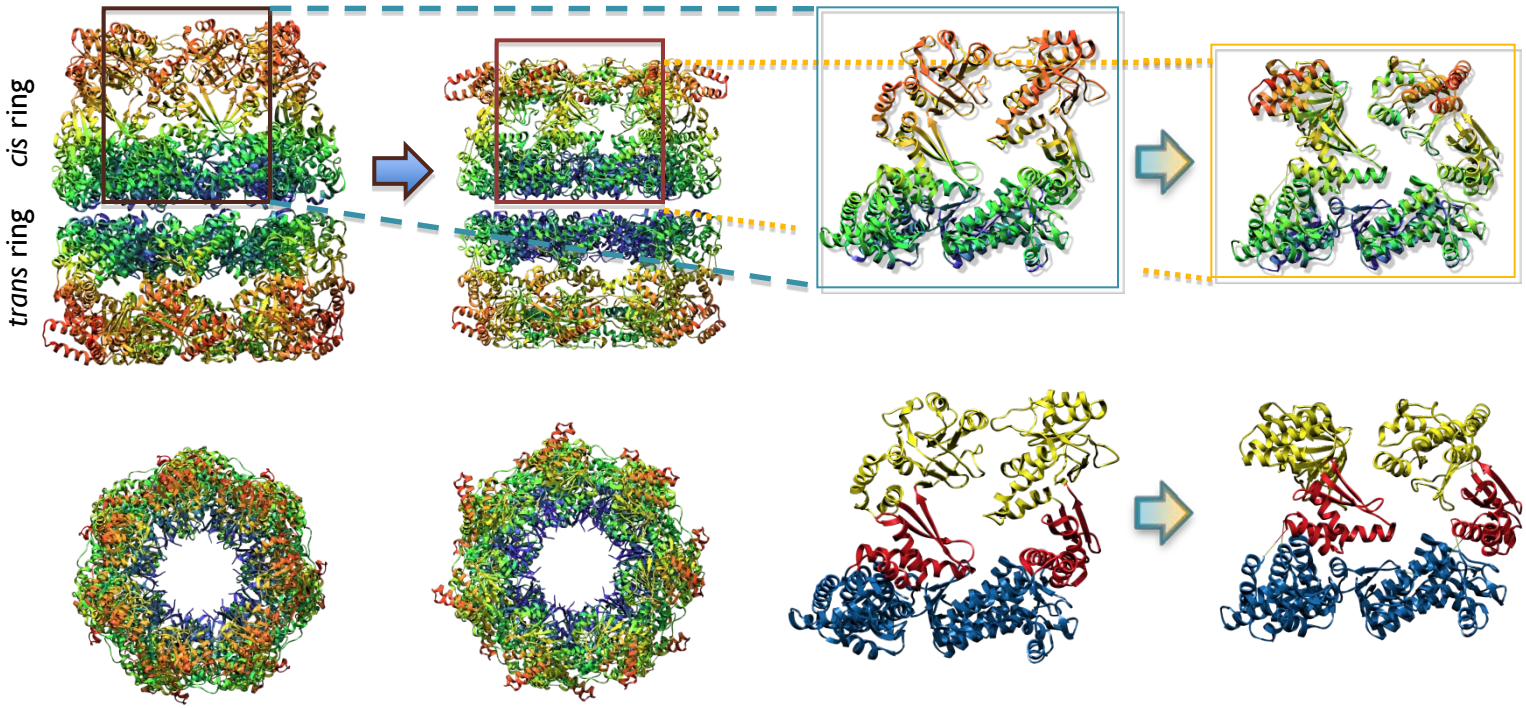
E461 mutant is a deformed structure along mode 1



E461K mutation causes disruption of inter-ring transfer of ATP-induced signal (Sewell et al NSB 2004)

Yang et al. *Mol Biosyst* 2008

Passage between the R and T state of GroEL



See...

Z Yang, P Marek and I Bahar, *PLoS Comp Biology* 2009

What is the overlap between computations and experiments?

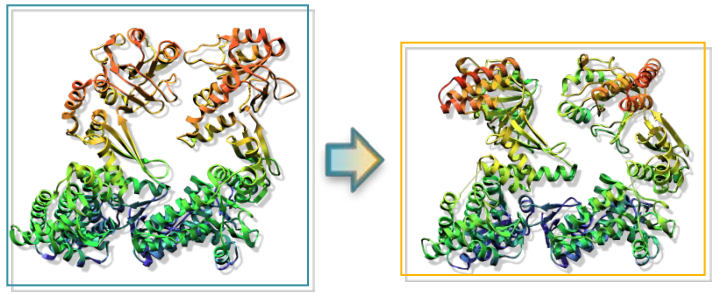
Computations

ANM yields a series of 3N dimensional deformation vectors

Mode 1 (slowest mode)
Mode 2
Mode 3
….
Mode 3N-6 (fastest mode)

Given by eigenvectors $\mathbf{u}_1, \mathbf{u}_2, \mathbf{u}_3, \ldots \mathbf{u}_{3N-6}$, with respective frequencies of $\lambda_1, \lambda_2, \lambda_3, \ldots \lambda_{3N-6}$

Experiments



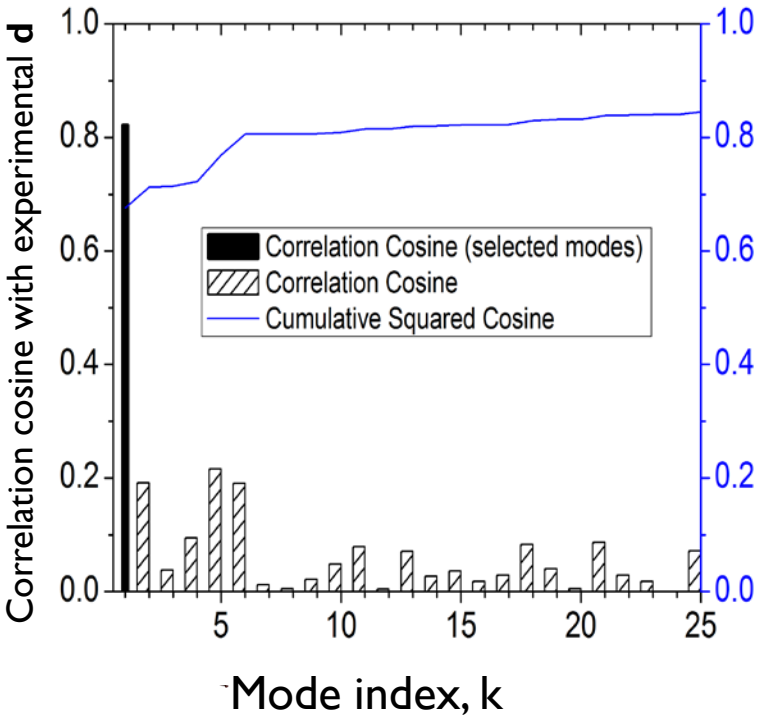
$$\mathbf{d} = [\Delta x_1 \;\; \Delta y_1 \;\; \Delta z_1 \;\ldots\;\; \Delta z_N]^T$$

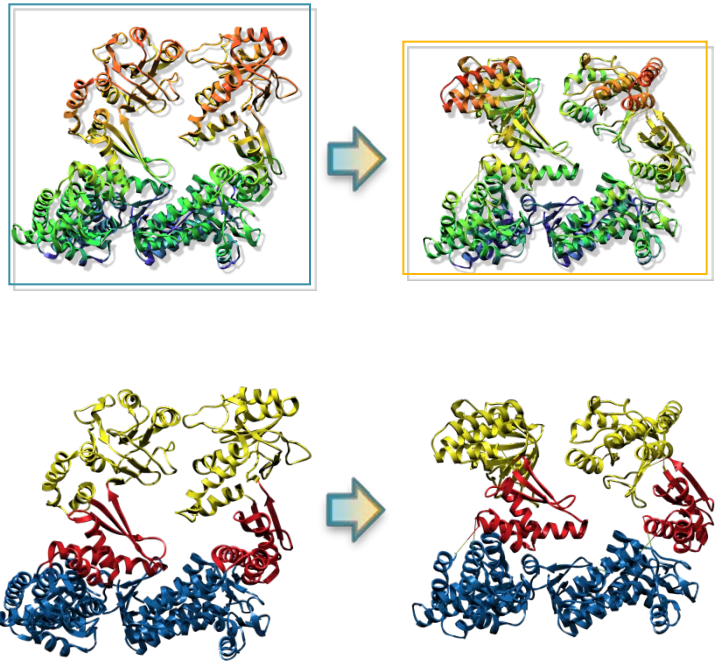
See...

Z Yang, P Marek and I Bahar, *PLoS Comp Biology* 2009

What is the overlap between computations and experiments?

Correlation cosine between u_k and d





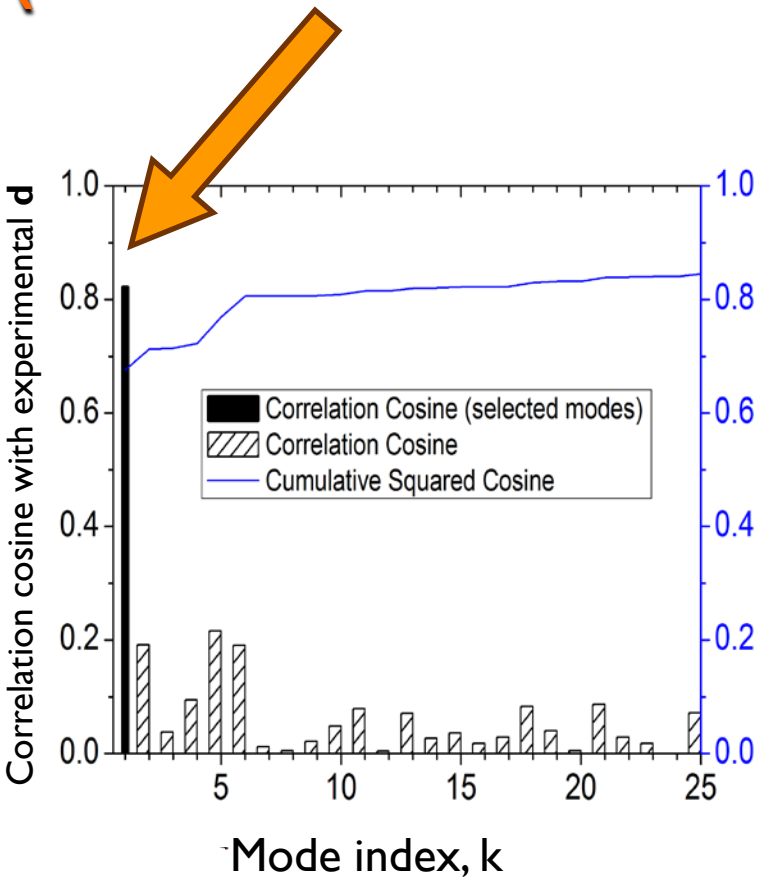
$\mathbf{d} = [\Delta x_1 \ \Delta y_1 \ \Delta z_1 \ \ldots \ \Delta z_N]^T$

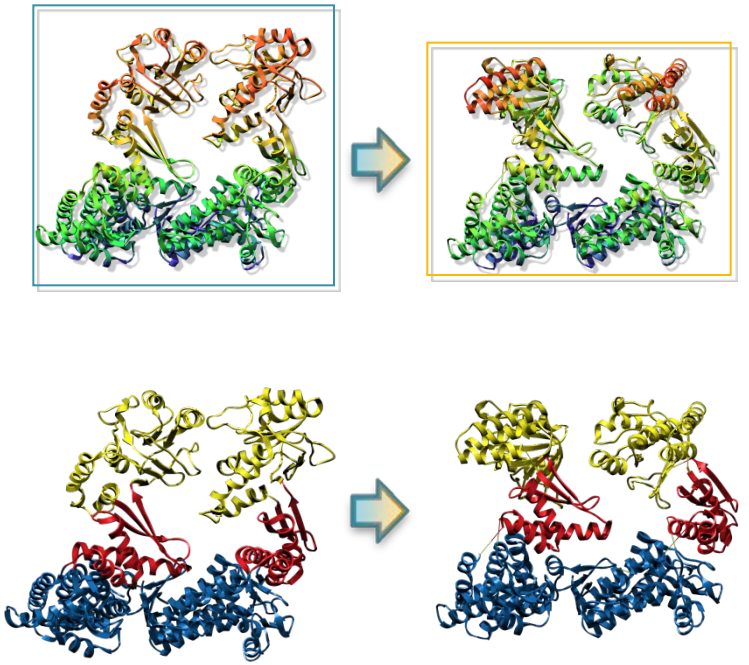
See...

Z Yang, P Marek and I Bahar, *PLoS Comp Biology* 2009

The softest mode enables the passage R → T

(with a correlation of 0.81)





$\mathbf{d} = [\Delta x_1 \ \Delta y_1 \ \Delta z_1 \ \ldots \ \Delta z_N]^T$

See...

Z Yang, P Marek and I Bahar, *PLoS Comp Biology* 2009

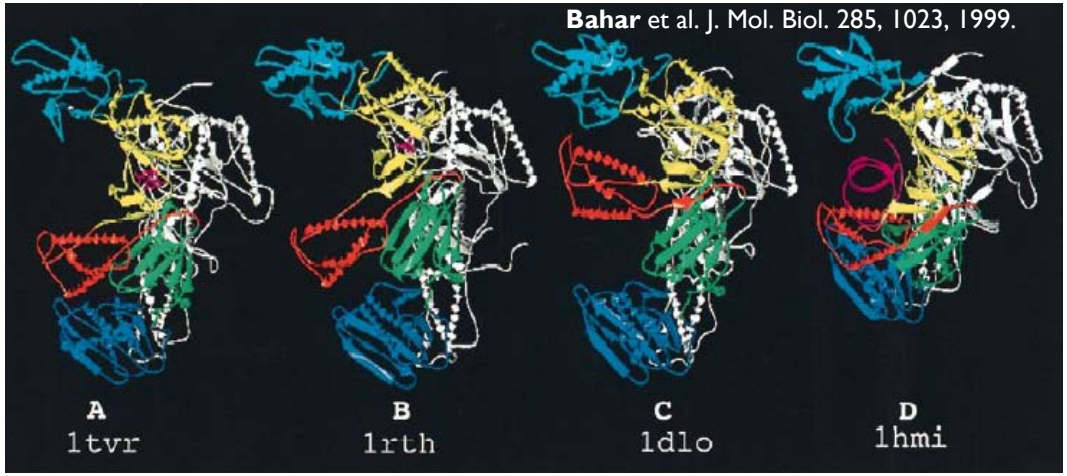
A better comparison

Consider more than 2 end points for a given structure, but all the **known structures for a given protein**

Ensembles of structures

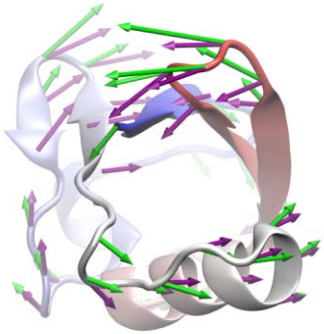
Dynamics inferred from known structures

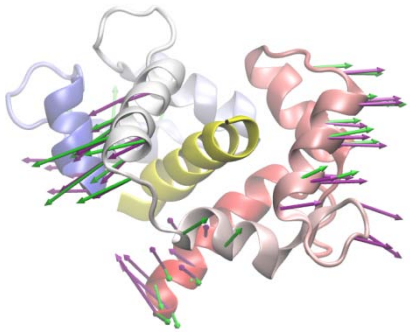
Comparison of static structures available in the PDB for the same protein in different form has been widely used is an **indirect** method of inferring dynamics.



Different structures resolved for HIV-1 reverse transcriptase (RT)

Global motions inferred from theory and experiments

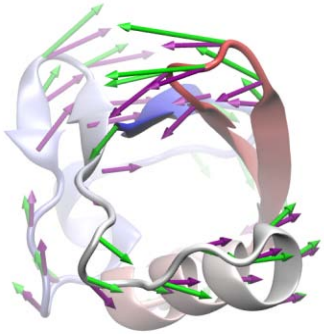


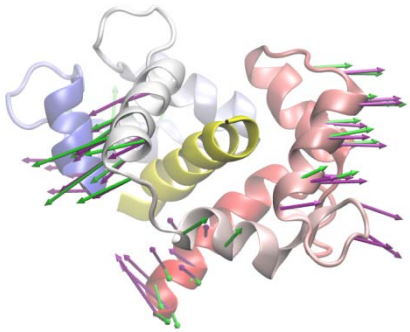


→ PCA of the ensemble of resolved structures

→ ANM analysis of a single structure from the ensemble

Global motions inferred from theory and experiments

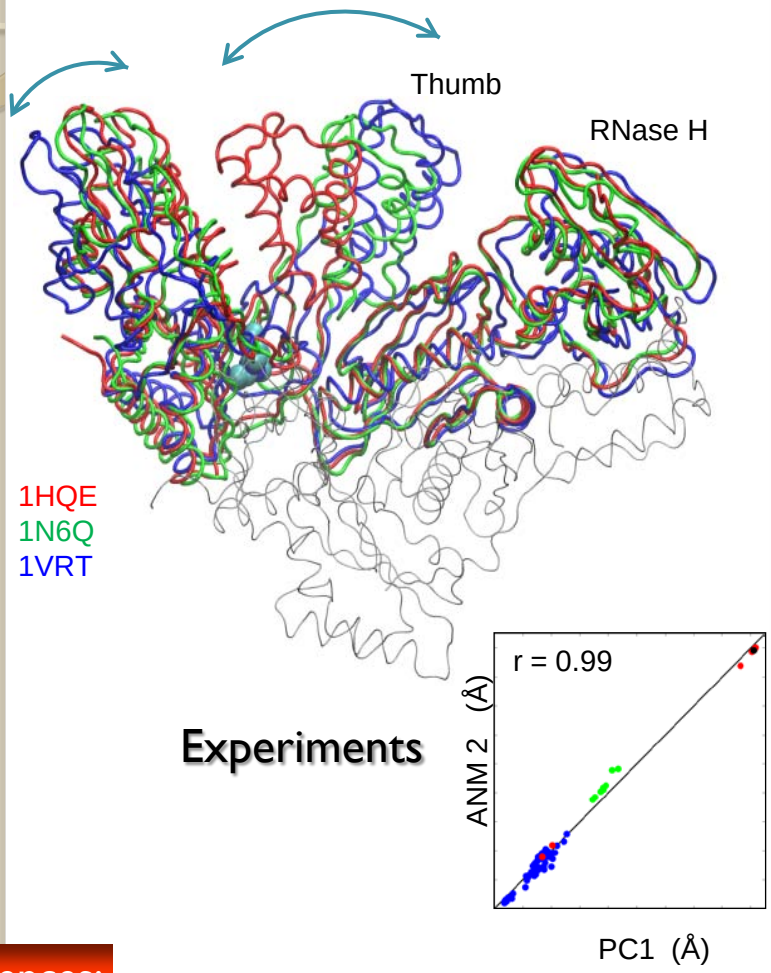




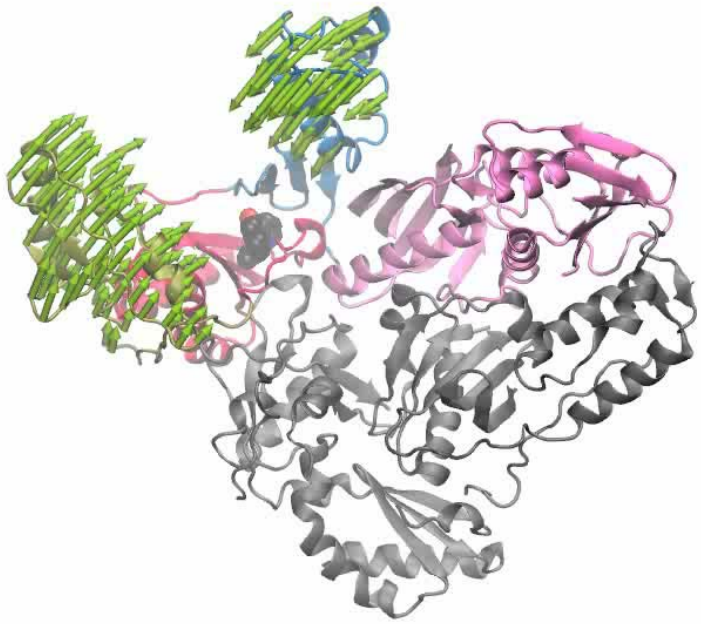
Reference:

*Bakan & Bahar (2009) PNAS **106**, 14349-54*

Induced Dynamics or Intrinsic Dynamics?



Experiments



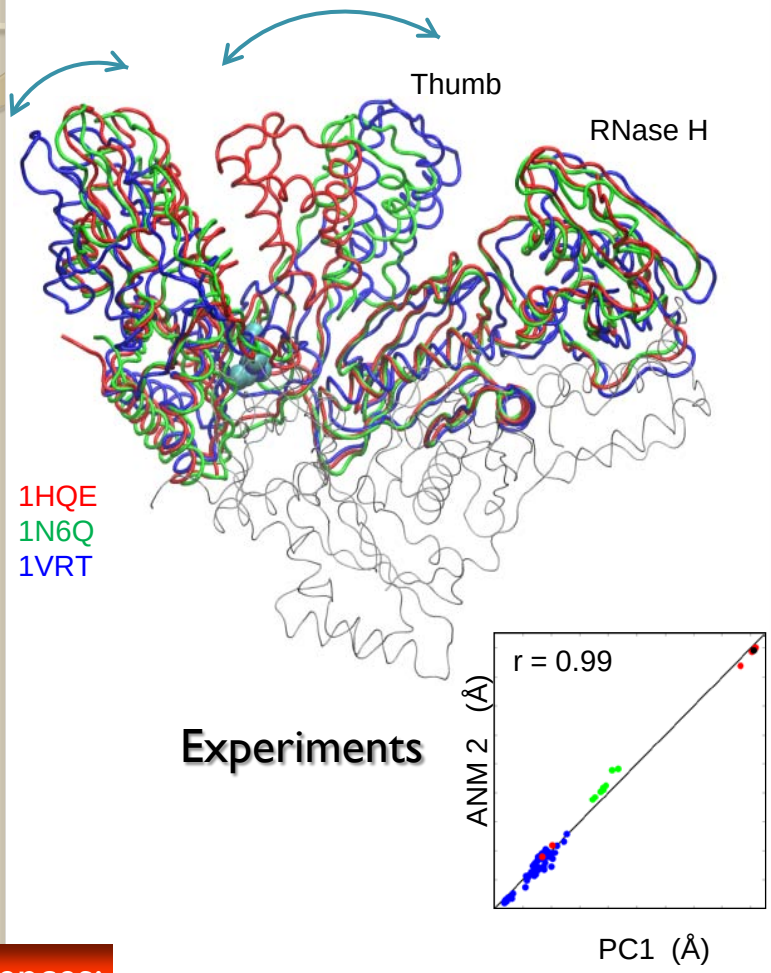
Theory

http://www.youtube.com/watch?v=1OUzdzm68YY

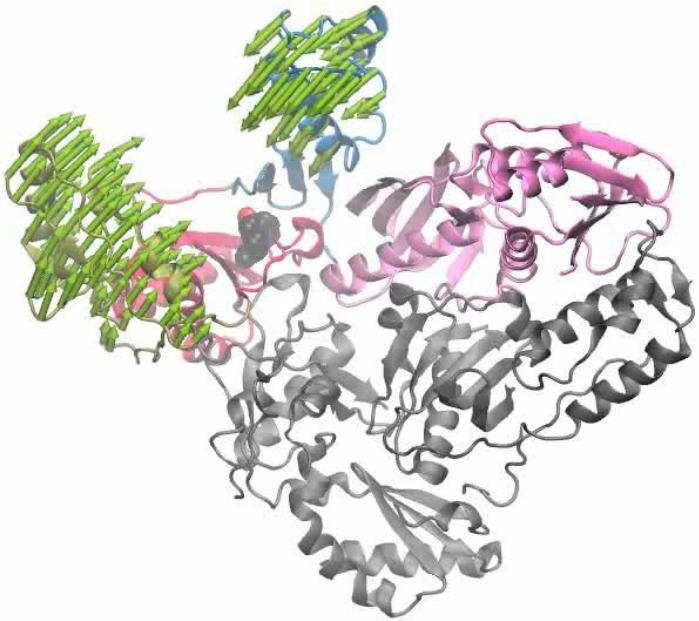
References:

Bakan & Bahar (2009) PNAS **106**, 14349-54.

Soft modes enable functional movements



Experiments



Theory

http://www.youtube.com/watch?v=1OUzdzm68YY

References:

Bakan & Bahar (2009) PNAS **106**, 14349-54.

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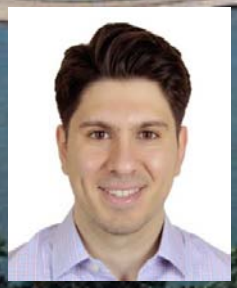
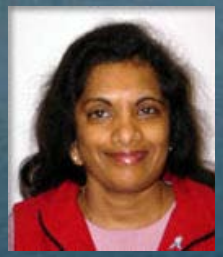


Dr. Mert Gur
Assist Prof, Istanbul Technical University

Cihan Kaya



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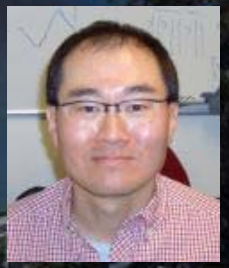

Dr. JiYoung Lee