ProDy

Protein Dynamics & Sequence Analysis

Overview & Applications

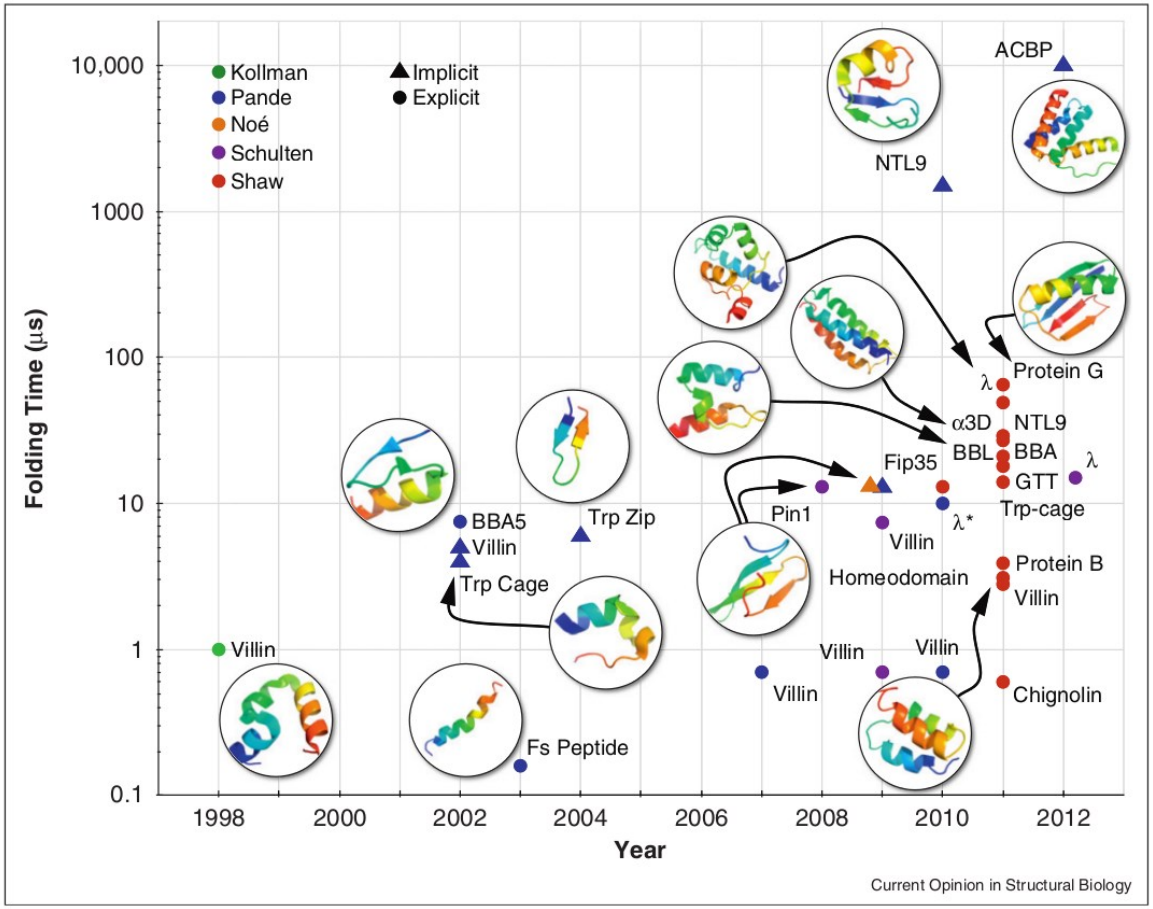
T. Lezon

Hands-on Workshop in Computational Biophysics

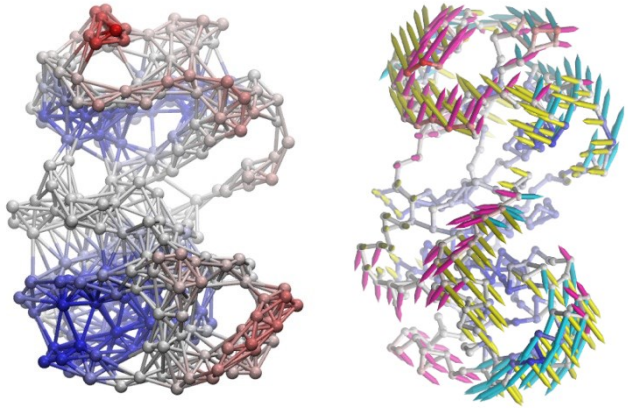
Pittsburgh Supercomputing Center

04 June, 2015

Simulations still take time



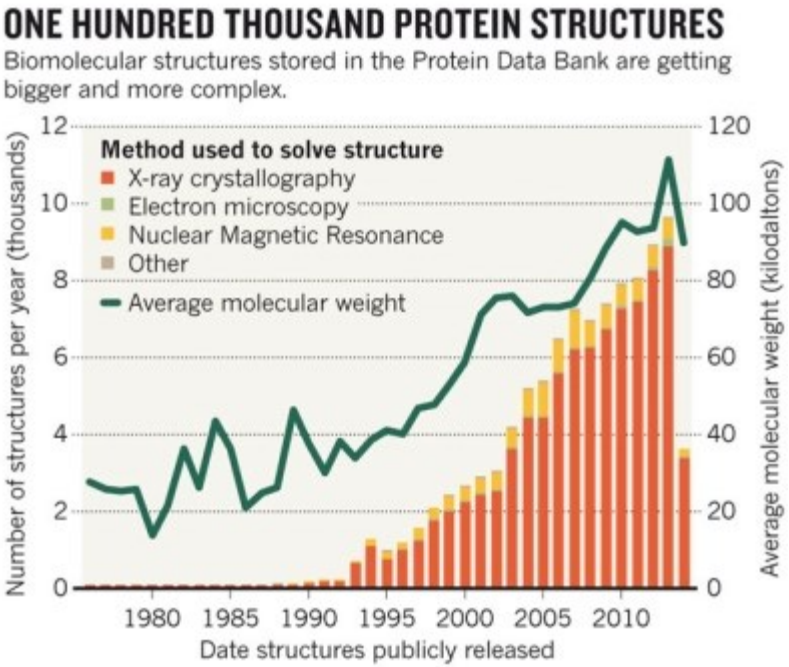
Lane et al. 2013



Bakan et al. Bioinformatics 2011.

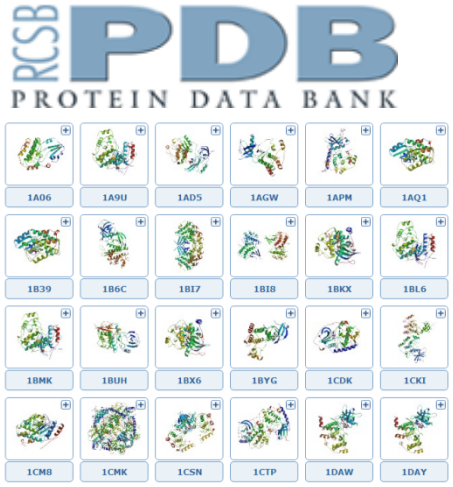
Coarse-grained Elastic Network Models are fast

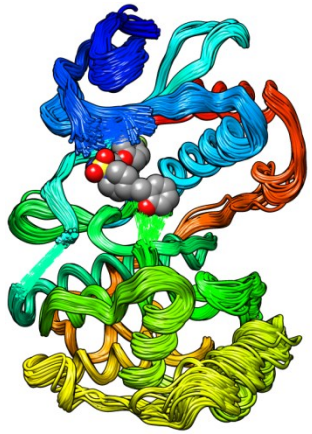
The structural data explosion



Nature, 15 May 2014.

Multiple structures for a single sequence

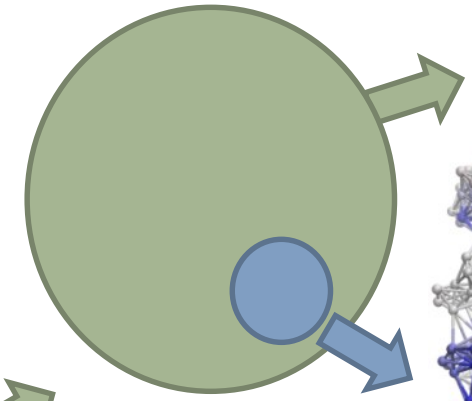


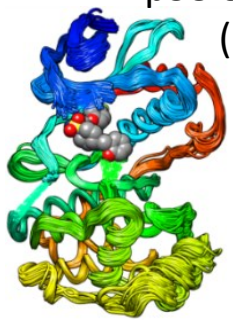


Dynamics may be inferred from structural data.

Exploiting the PDB since 2010

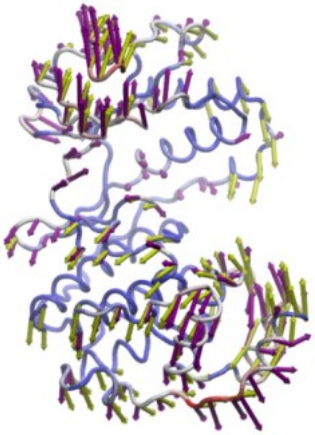
- High-throughput analysis of structural data
- Application Programming Interface (API) for development of tools
- Suitable for interactive usage

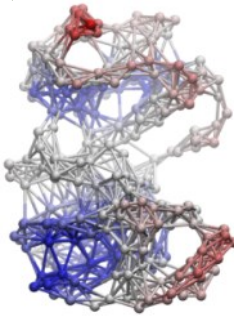




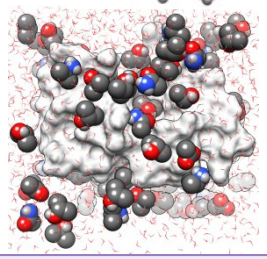
p38 ensemble (PCA)

Experiment/Theory





p38 network model (ANM)



MD trajectory analysis (EDA)

User inputs a sequence

Usage example

```
>1A9U:A|PDBID|CHAIN
GSSHHHHHHSSGLVPRGSHMSQ
ERPTFYRQELNKTIWEVPERYQ
NLSPVGSGAYGSVCAAFDTKTG
......
```

ProDy *identifies*, *retrieves*, *aligns*, and *analyzes (PCA)* structures matching input sequence

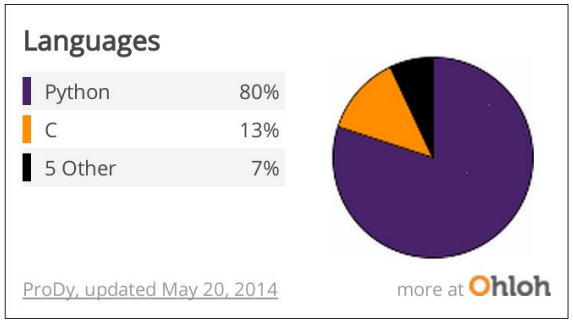
User can
- Compare experimental and theoretical models
- Sample conformations along normal modes

Bakan, Meireles & Bahar. Bioinformatics 2011.

ProDy
Protein Dynamics & Sequence Analysis

MMBioS

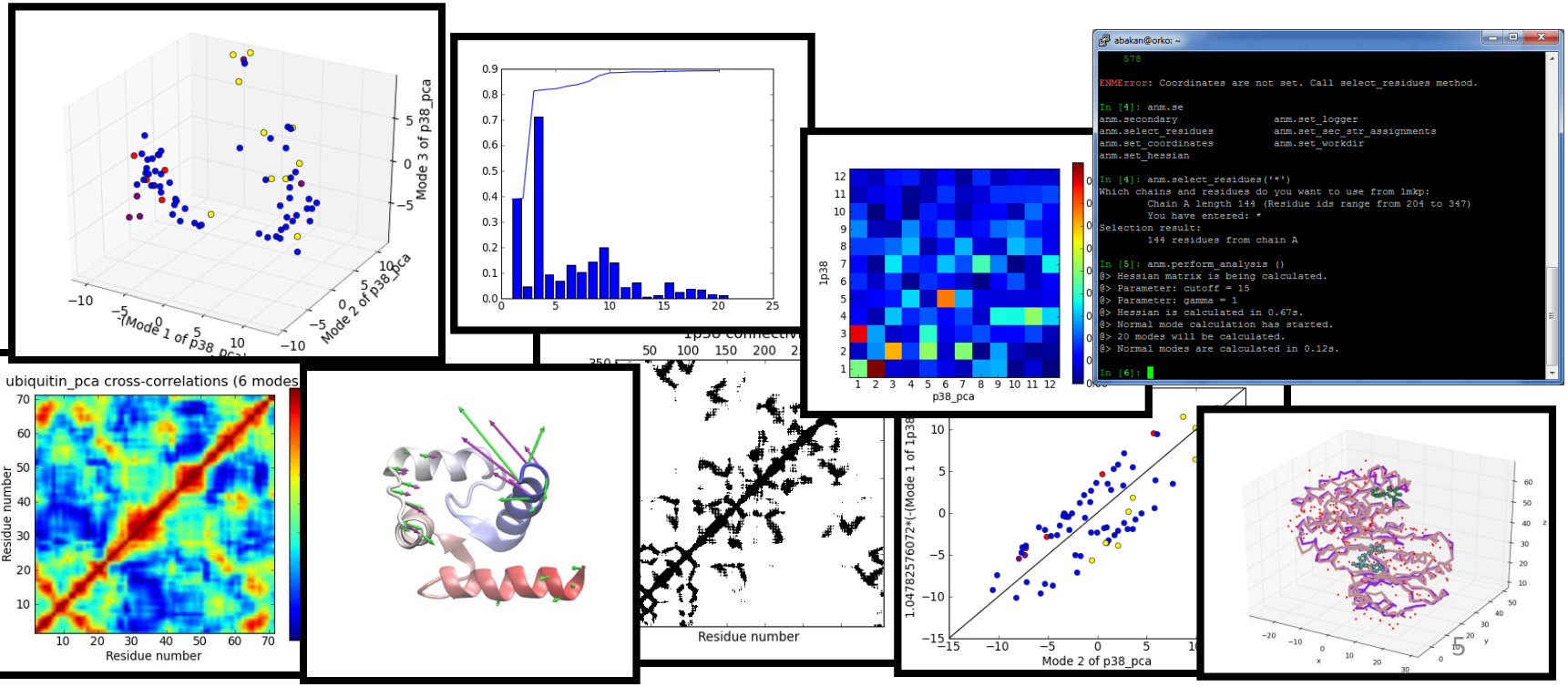
An Interactive Tool



matplotlib

NumPy

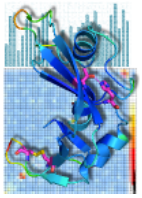
IP[y]: IPython
Interactive Computing



An evolving suite of tools

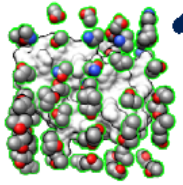
ProDy
Protein Dynamics & Sequence Analysis

- Principal Component Analysis
- Elastic Network Models
- Normal Mode Analysis
- Trajectory Analysis



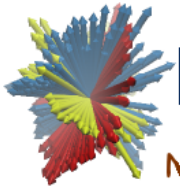
Evol
Bridging Evolution & Dynamics

- Multiple Sequence Alignment
- Correlated Mutation Analysis
- Structural Evolution



DruGUI
Druggability Suite for VMD

- Computational Drug Discovery
- Binding Site Prediction
- Affinity Estimation



NMWiz
Normal Mode Wizard for VMD

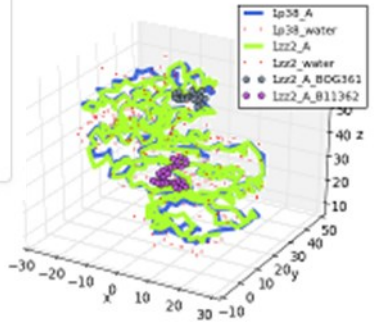
- Call ProDy from VMD
- Normal Mode Visualization

Tutorials: ProDy & Structure Analysis

ProDy

Learn how to use ProDy from the introductory ProDy tutorial or from the comprehensive API reference manual.

Tutorial | Manual



Structure Analysis

Learn how to compare and align structures, identify ligand contacts, and extract ligands from PDB files.

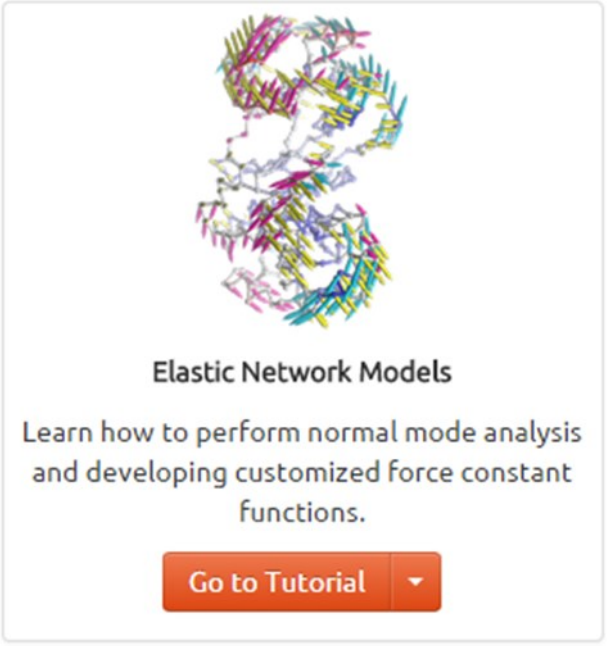
Go to Tutorial

- Obtaining PDB Files
- BLAST Searching the PDB
- Constructing Biomolecules from Transformations
- Aligning and Comparing Structures
- Identifying Intermolecular Contacts

ProDy
Protein Dynamics & Sequence Analysis

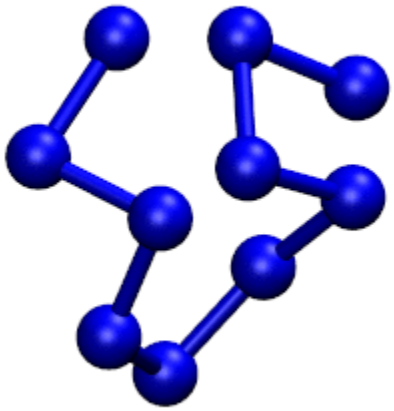
MMBioS

Tutorial: Elastic Network Models



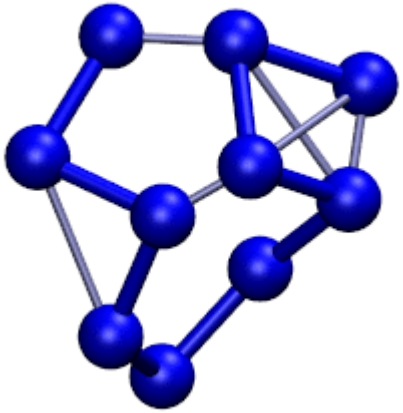
- Gaussian Network Model (GNM)
- Anisotropic Network Model (ANM)
- Normal Mode Algebra
- Deformation Analysis
- Customizing ENMs

Elastic Network Model



- Useful for finding global equilibrium motions of proteins
- Employs harmonic potential about native state
- Coarse-grained (Cα-only description)
- Residue pairs are connected via springs
- Normal modes are found analytically

Elastic Network Model



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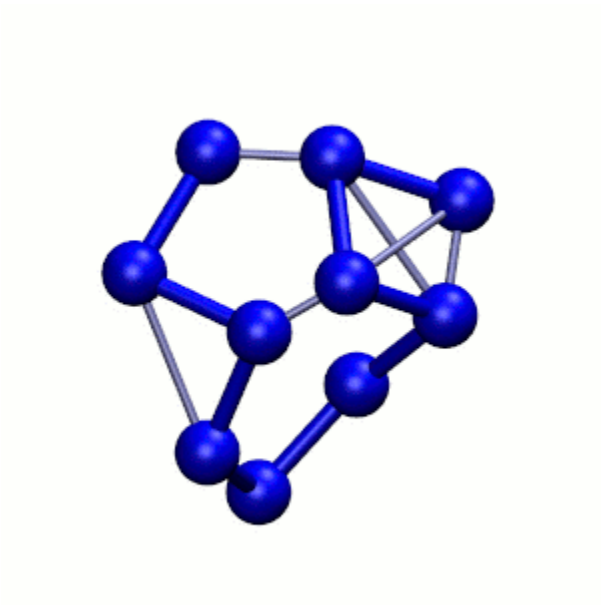
Elastic Network Model



- Useful for finding global equilibrium motions of proteins
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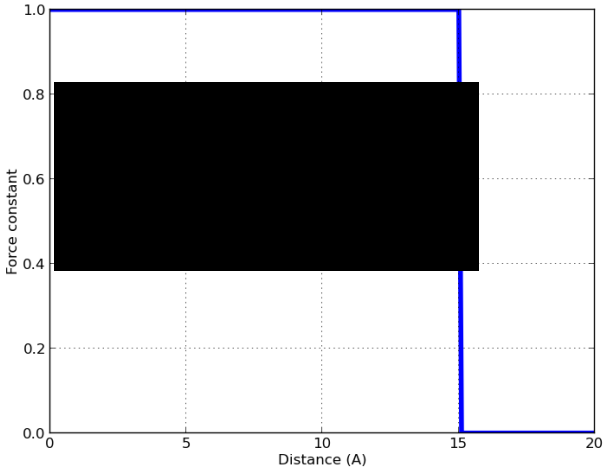
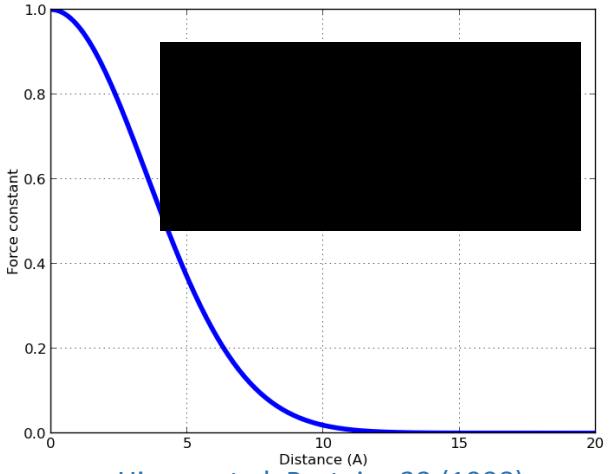
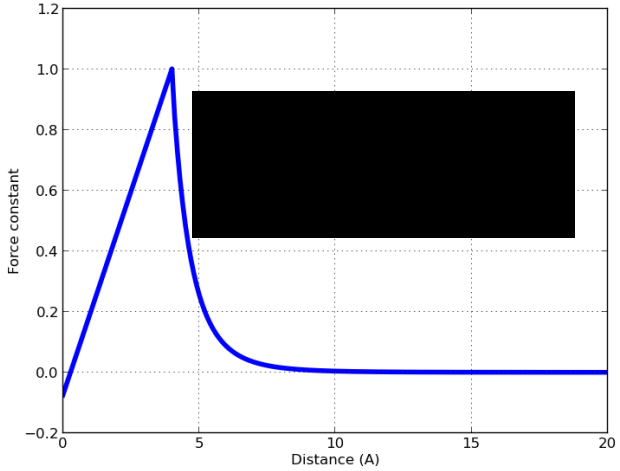
Flexible force constants



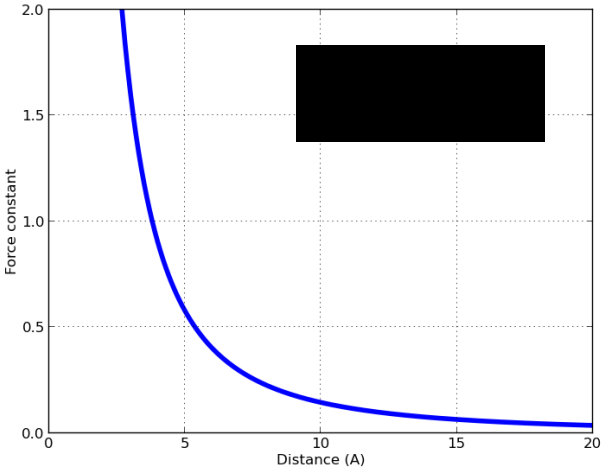
Tirion, PRL 77 (1996).



Hinsen et al. Proteins 33 (1998).



Hinsen et al. Chem Phys 261 (2000).

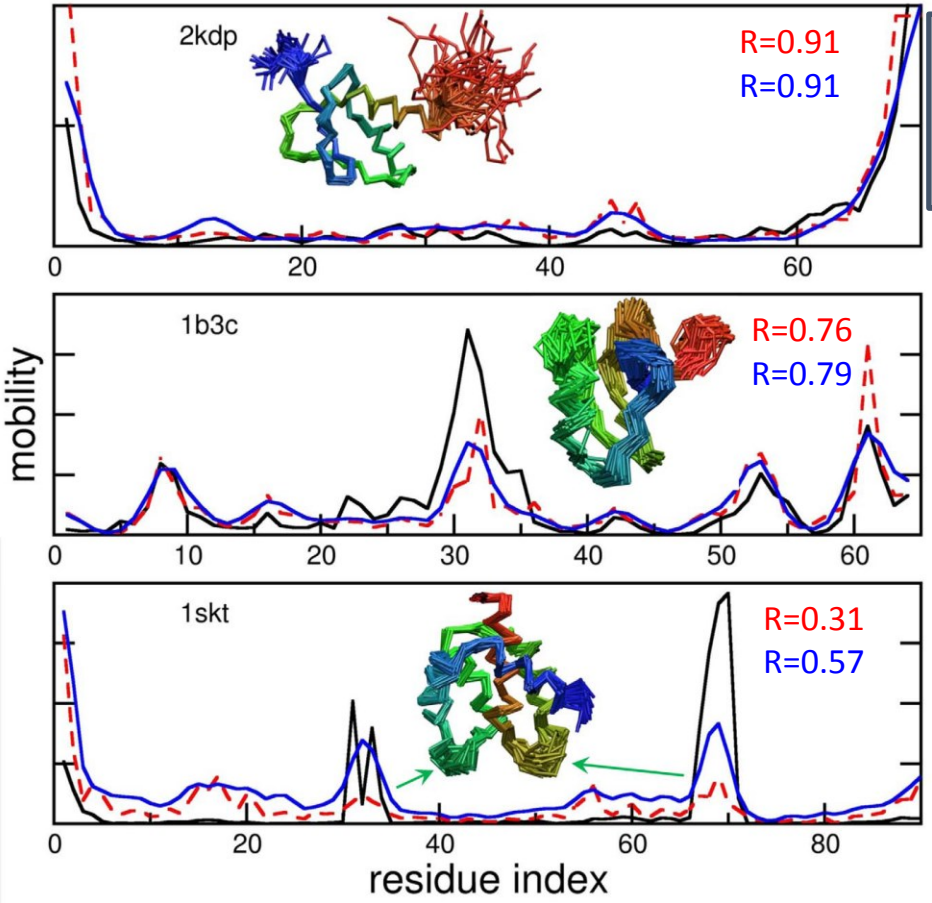


Yang et al. PNAS 106 (2009).

Optimizing force constants

- Download NMR structures from PDB — fetchPDB()
- Calculate residue MSFs for each protein — calcMSF()
- Assign ENM topology — buildHessian()
- Optimize force constants to reproduce structural dynamics
- Search for trends in force constant values with structure

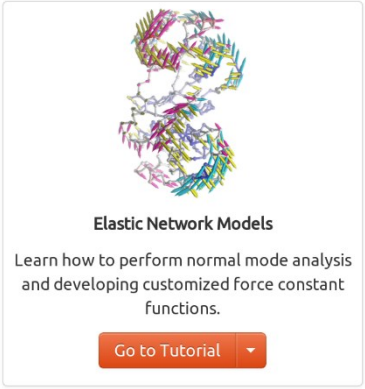
Fine-tuning force constants



- Distance-dependence
- 1st neighbors
- 2nd neighbors
- H bonds

black: NMR
red: ENM
blue: modified ENM

GammaStructureBased()



Learn more at prody.csb.pitt.edu

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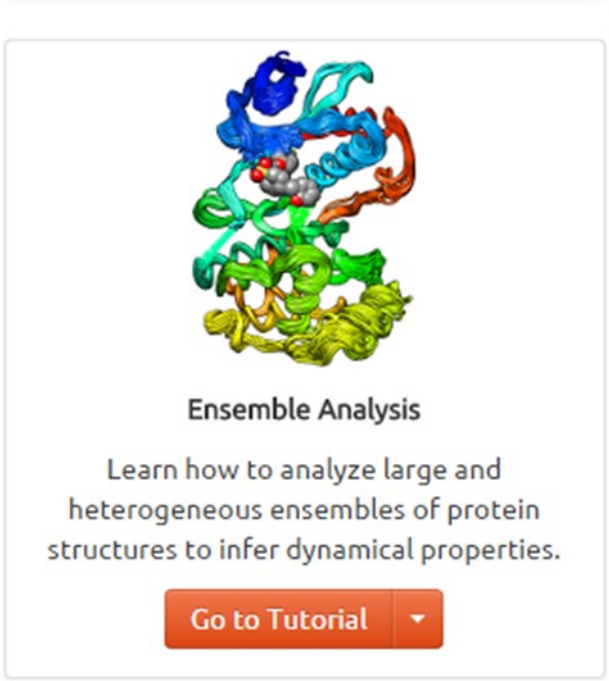
MMBioS

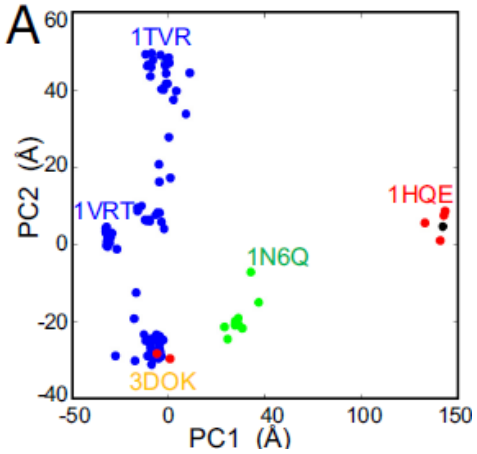
Tutorial: Ensemble Analysis

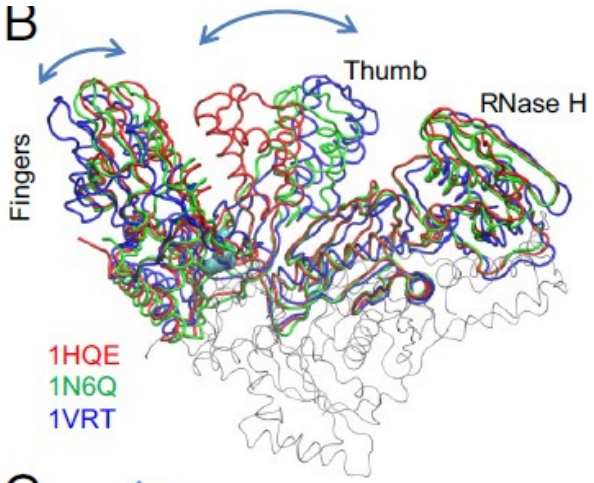


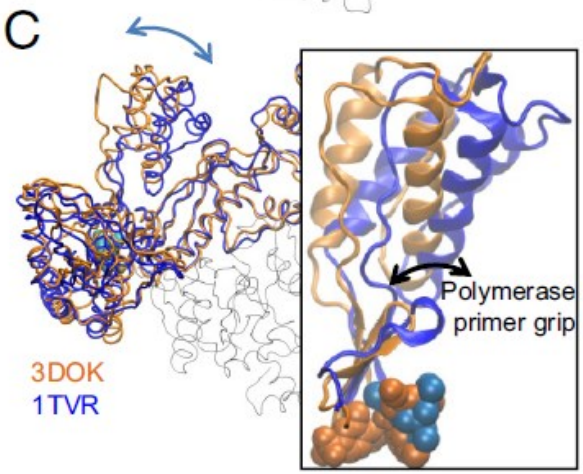
- NMR Models
- Homologous Proteins
- Multiple X-ray Structures
- Multimeric Proteins

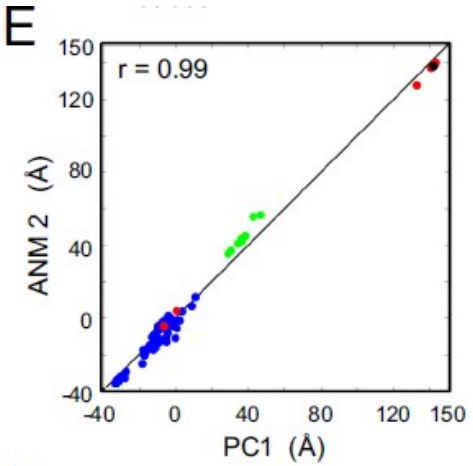
Example: Comparing PCA and ENM

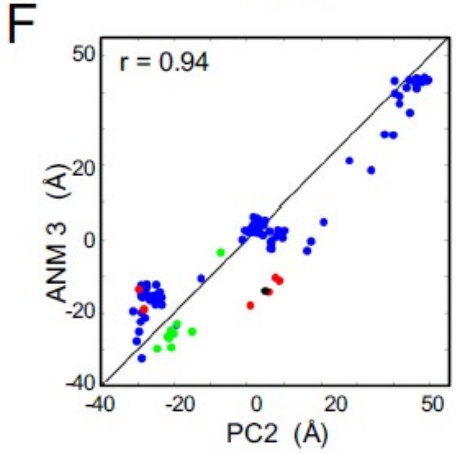
Structures of HIV1-RT
Unbound
Inhibitor bound
DNA bound







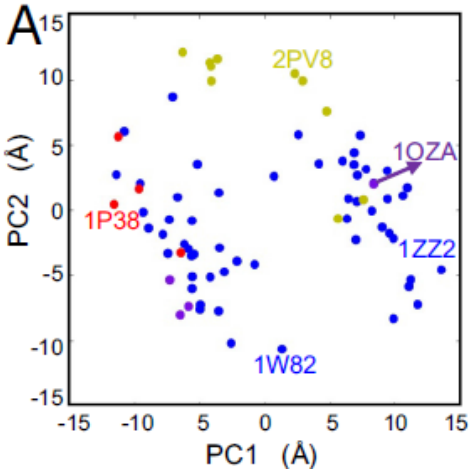


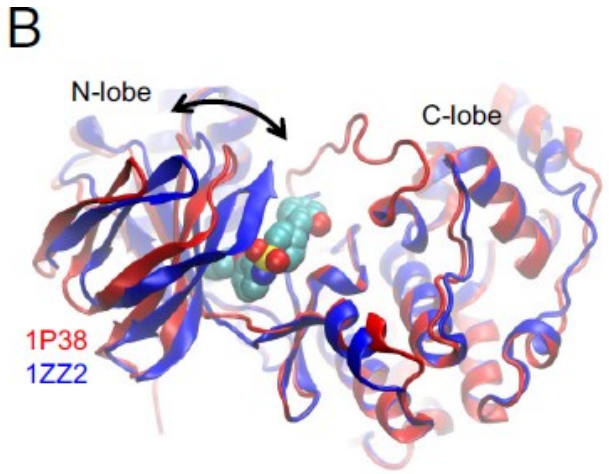


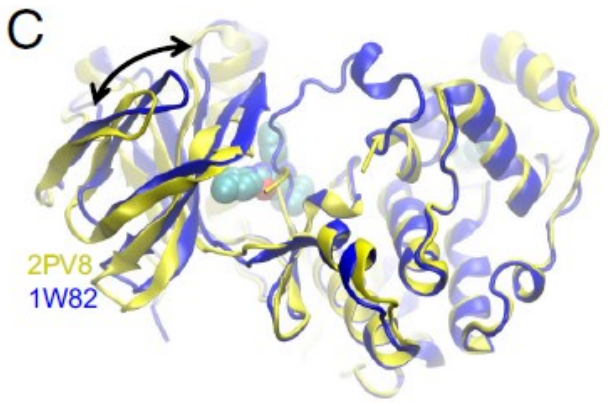
Bakan & Bahar. PNAS 106 (2009).

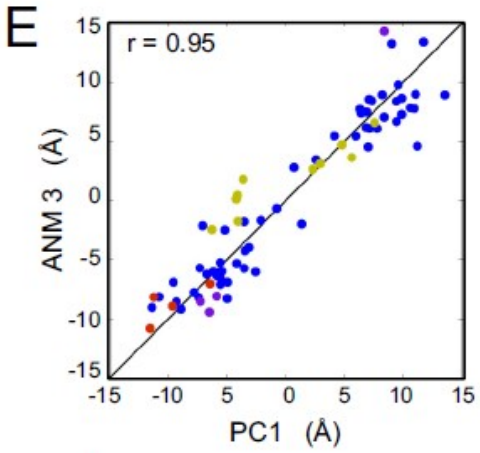
Example: Comparing PCA and ENM

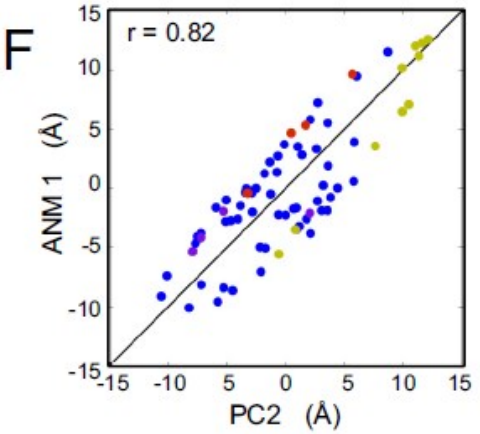
Structures of p38 MAPK
Unbound
Inhibitor bound
Glucose bound
Peptide bound





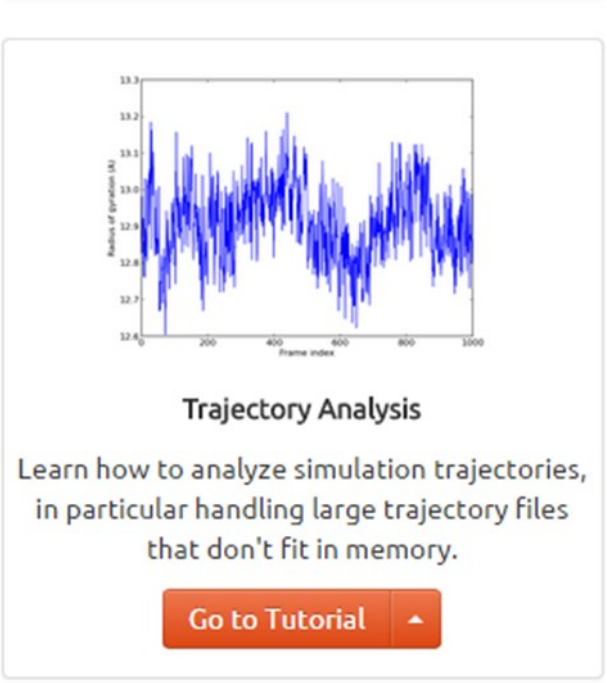






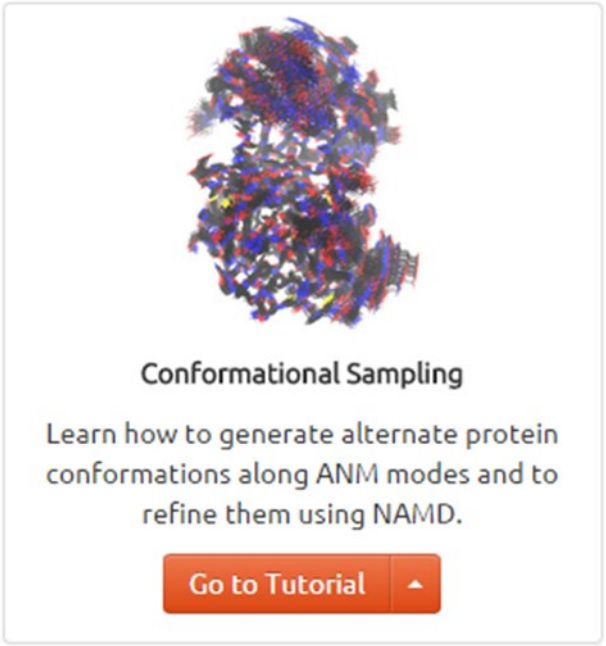
Bakan & Bahar. PNAS 106 (2009).

Tutorial: Trajectory Analysis



- Fast processing of long trajectories
- Enables comparison of MD trajectories and structural data or ENM results

Tutorial: Conformational Sampling

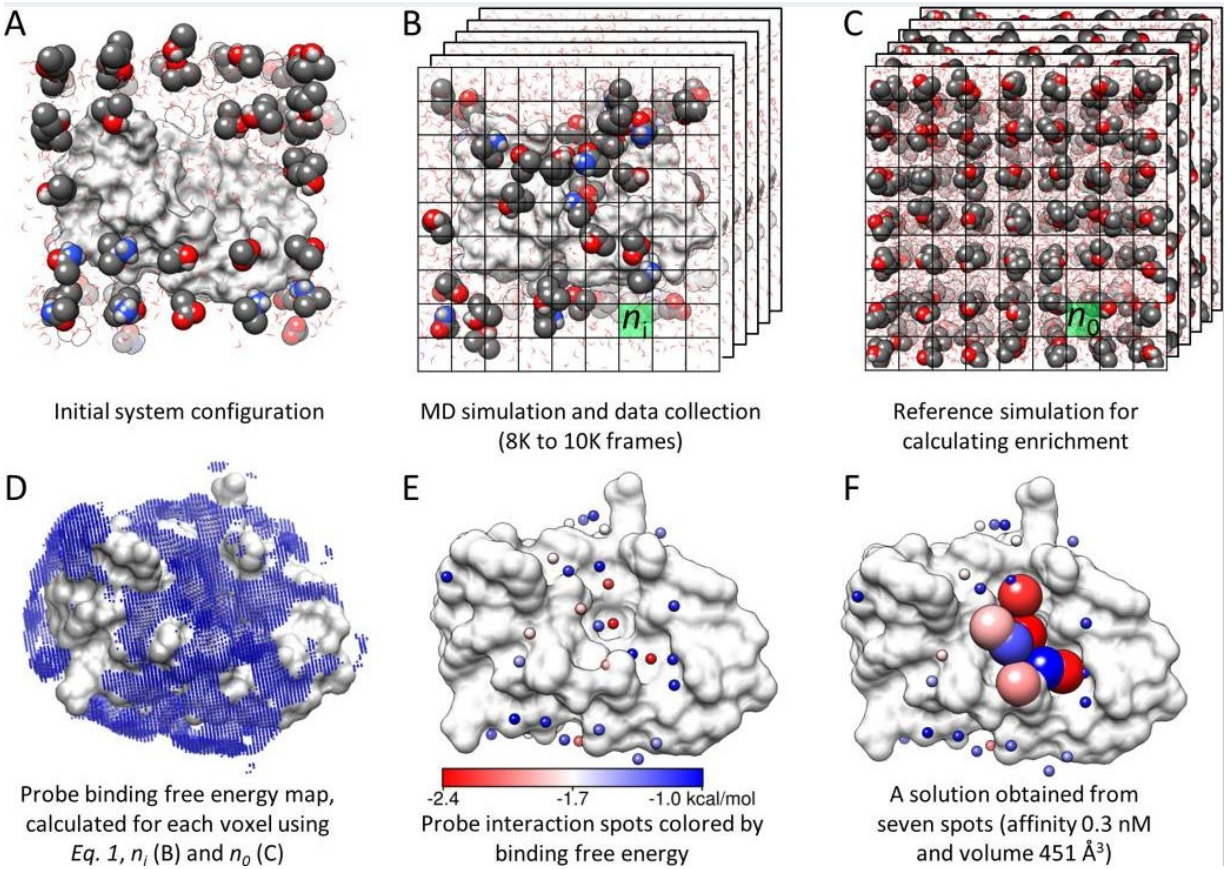


- Sample structures along normal modes
- Refine structures using NAMD

Tutorial: Druggability

- Set up NAMD simulations
- Analyze trajectories to identify binding hot spots

Exploring binding with probe molecules



Bakan et al. J Chem Theor Comput (2012).

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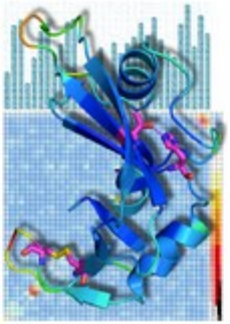
MMBioS

Tutorial: Evol



Evol

Learn how to identify conserved and coevolved residues and characterizing their dynamical properties.

Go to Tutorial

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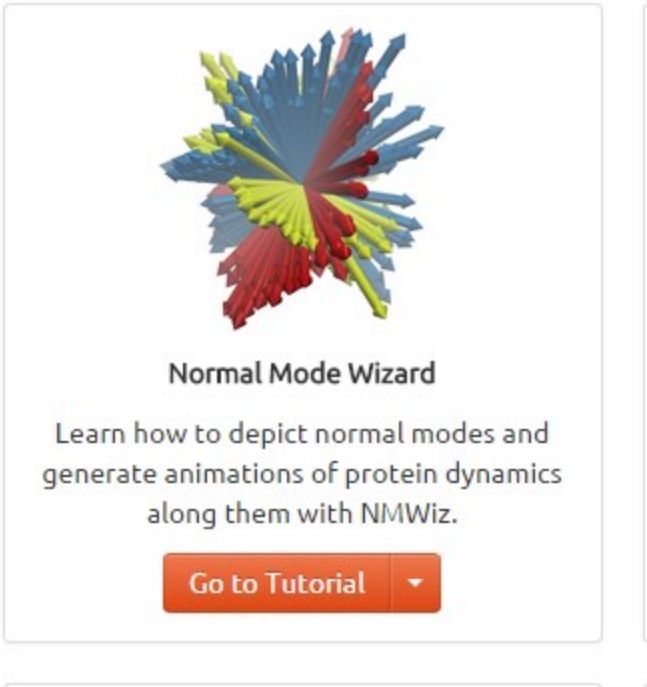
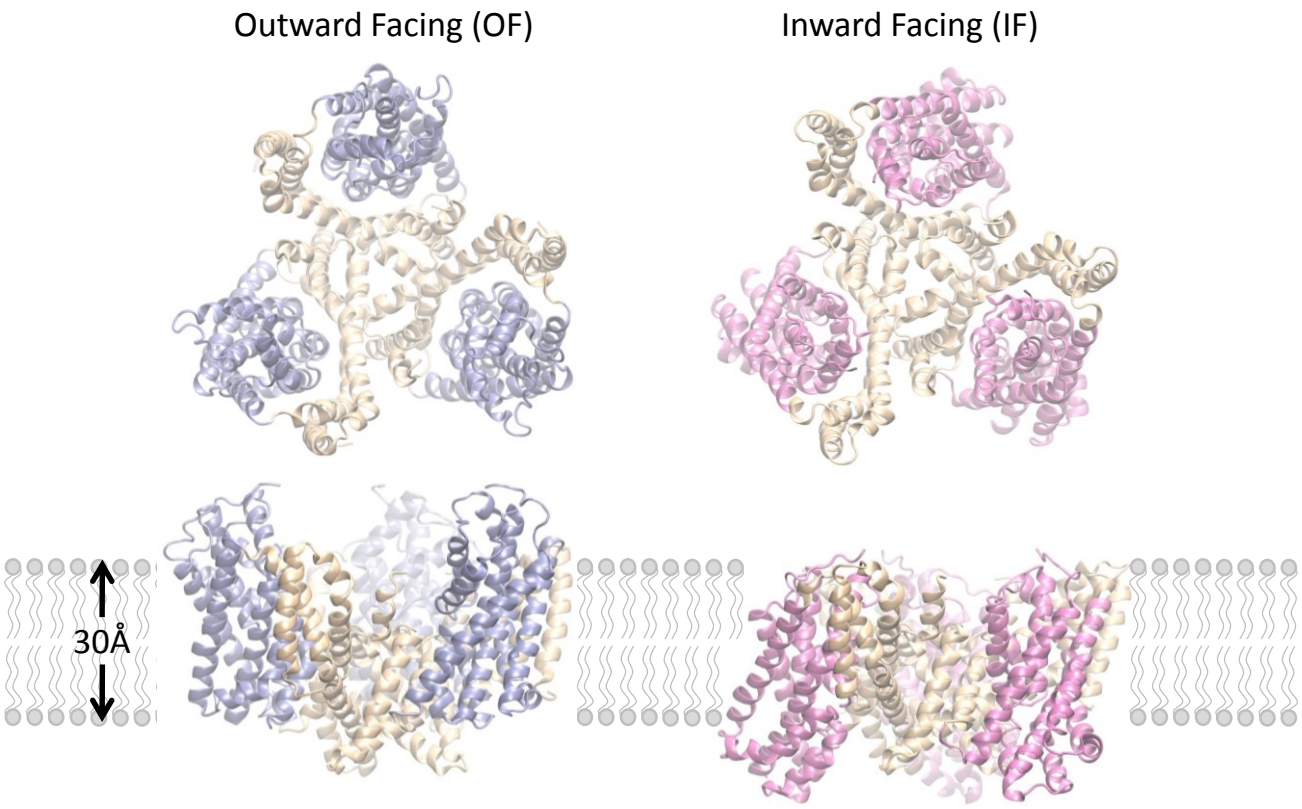
Tutorial: Normal Mode Wizard



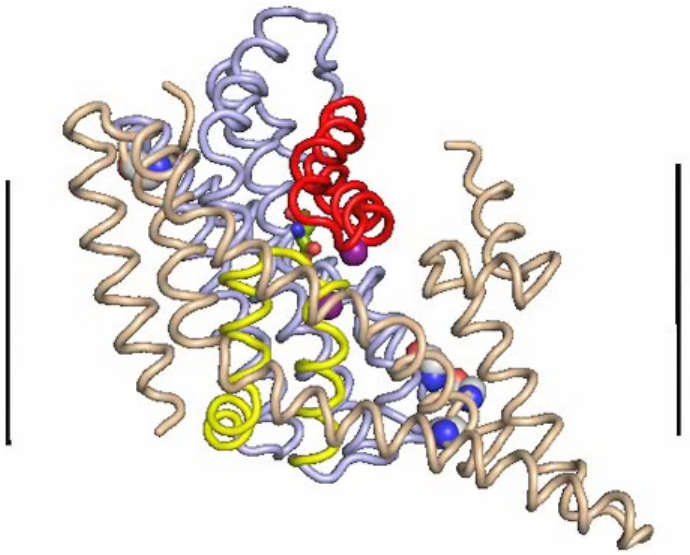
Global transitions



Yernool *et al*. Nature 431 (2004).
Reyes *et al*. Nature 462 (2009).

Global transitions

Single subunit showing the transport domain moving across the membrane



Reyes *et al*. Nature 462 (2009).

Rotations-Translations of Blocks

H^{RTB} = P

$(6N_b \times 6N_b)$ $(6N_b \times 3N)$

H^{AA} $(3N \times 3N)$ P^T $(3N \times 6N_b)$

Smaller Hessian can be more easily diagonalized...

V'^{AA} = P^T V^{RTB}

...and modes projected back into all-residue space

H: ANM Hessian (3 rows/cols per residue)
P: Projection matrix from all-residue space to rigid block space
H^{RTB}: RTB Hessian (no internal motions of blocks)
V'^{AA}: Approximate ANM motions

RTB.buildHessian()

Ming & Wall. PRL 95 (2005).
Zheng & Brooks. Biophys J 89 (2005).

Exploring structural transitions: Glutamate transporter

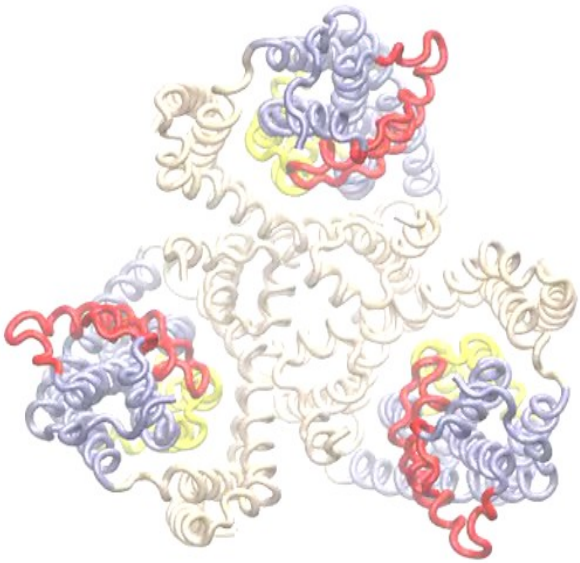
ANM predicts large radial motions of the trimer. Can we invent a better model?

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

Altered radial force constants:

$$\mathbf{H}_{ij} = -\left(R_{ij}^0\right)^{-2}\begin{bmatrix} \left(x_{ij}^0\sqrt{\gamma_x}\right)^2 & x_{ij}^0 y_{ij}^0\sqrt{\gamma_x\gamma_y} & x_{ij}^0 z_{ij}^0\sqrt{\gamma_x\gamma_z} \\ x_{ij}^0 y_{ij}^0\sqrt{\gamma_x\gamma_y} & \left(y_{ij}^0\sqrt{\gamma_y}\right)^2 & y_{ij}^0 z_{ij}^0\sqrt{\gamma_y\gamma_z} \\ x_{ij}^0 z_{ij}^0\sqrt{\gamma_x\gamma_z} & y_{ij}^0 z_{ij}^0\sqrt{\gamma_y\gamma_z} & \left(z_{ij}^0\sqrt{\gamma_z}\right)^2 \end{bmatrix}$$

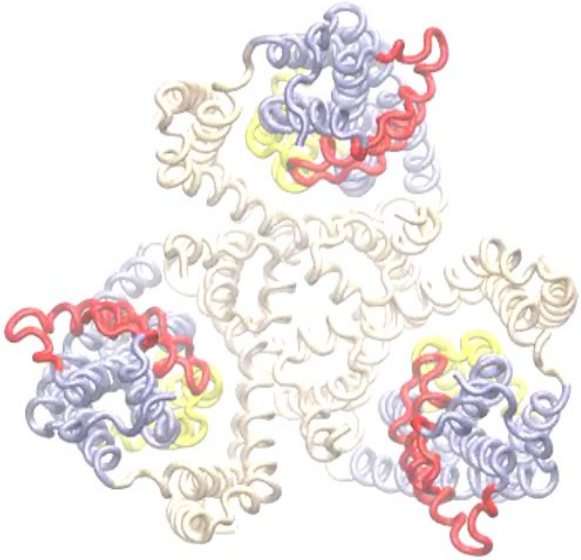
$$\mathbf{H}_{ij} = -\frac{\gamma}{\left(R_{ij}^0\right)^2}\begin{bmatrix} \left(x_{ij}^0\right)^2 & x_{ij}^0 y_{ij}^0 & cx_{ij}^0 z_{ij}^0 \\ x_{ij}^0 y_{ij}^0 & \left(y_{ij}^0\right)^2 & cy_{ij}^0 z_{ij}^0 \\ cx_{ij}^0 z_{ij}^0 & cy_{ij}^0 z_{ij}^0 & \left(cz_{ij}^0\right)^2 \end{bmatrix}$$



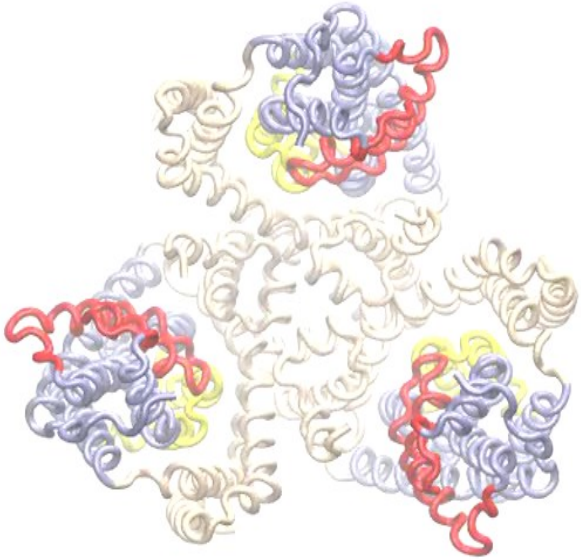
RTB.buildHessian()

Lezon & Bahar. Biophys J 102 (2012).

Exploring structural transitions: Glutamate transporter

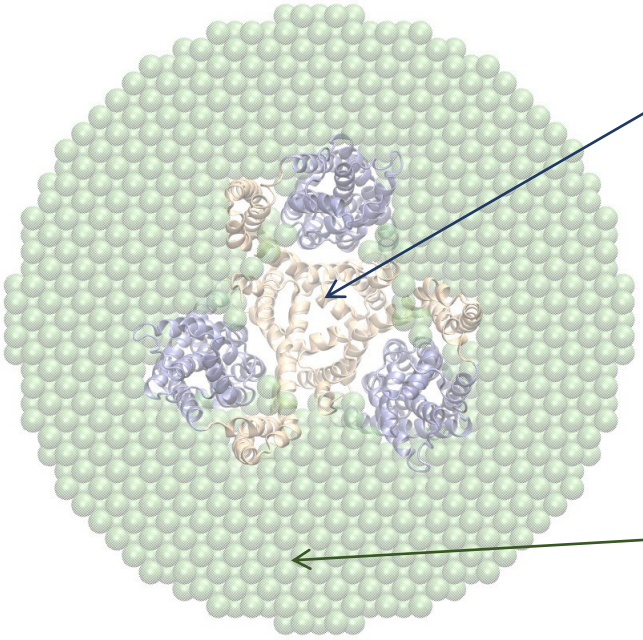


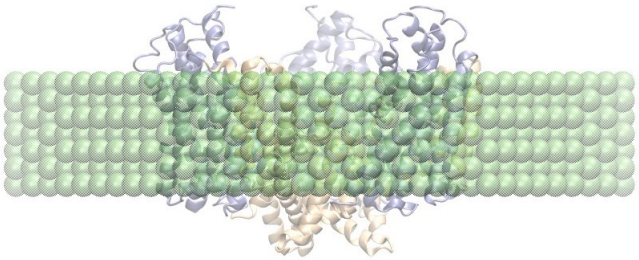
ANM: Large radial motions

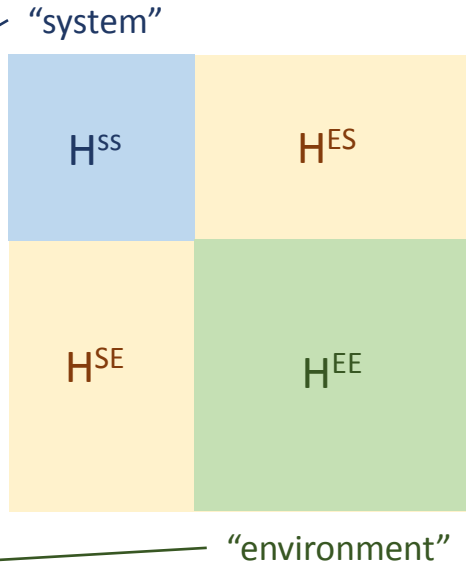


imANM

Explicit membrane models







As the *environment* fluctuates randomly, the effective motion of the *system* is given by

reduceModel()