Applications of normal modes in structural dynamics

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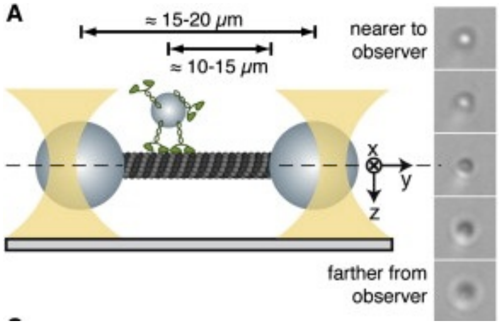
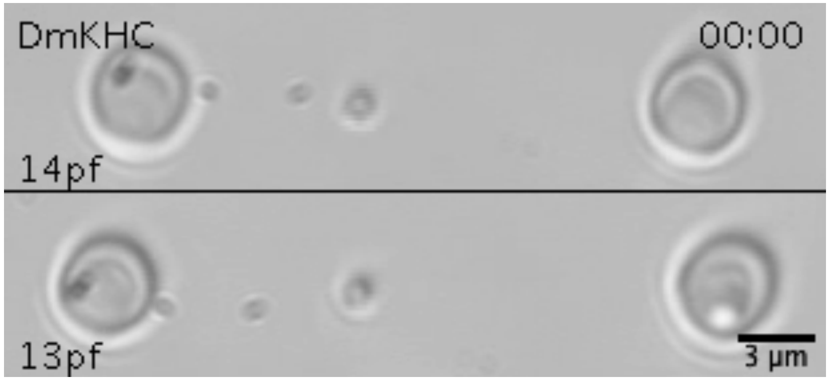
Real-time motion of kinesin on a microtubule





~10 μ m/10s = 1nm/ms

Brunnbauer et al. Mol Cel 46:147 (2012).

Approximating the protein free energy landscape

Rough and funnel-shaped energy landscape that is function of atomic coordinates

$$\mathbf{r} = (x_1, y_1, z_1, \ldots, x_N, y_N, z_N)^T$$

$$\Delta\mathbf{r} = \mathbf{r} - \mathbf{r}^0$$

$$V(\mathbf{r}) = V(\mathbf{r}^0) + \sum_i \left(\frac{\partial V}{\partial r_i}\right)_{\mathbf{r}^0} \Delta r_i + \tfrac{1}{2} \sum_{ij} \left(\frac{\partial^2 V}{\partial r_i \partial r_j}\right)_{\mathbf{r}^0} \Delta r_i \Delta r_j + \tfrac{1}{6} \sum_{ijk} \left(\frac{\partial^3 V}{\partial r_i \partial r_j \partial r_k}\right)_{\mathbf{r}^0} \Delta r_i \Delta r_j \Delta r_k + \ldots$$

$$V(\mathbf{r}) \approx \tfrac{1}{2} \sum_{ij} \left(\frac{\partial^2 V}{\partial r_i \partial r_j}\right)_{\mathbf{r}^0} \Delta r_i \Delta r_j$$

$$= \tfrac{1}{2} \Delta\mathbf{r}^T \mathcal{H} \Delta\mathbf{r}$$

denatured

E

native

Equations of Motion

$$\mathbf{M}\Delta\ddot{\mathbf{r}} = -\mathcal{H}\Delta\mathbf{r}$$

Newton

$$\left\{\begin{array}{l} \mathbf{q} = \mathbf{M}^{1/2}\Delta\mathbf{r} \\ \mathbf{H} = \mathbf{M}^{-1/2}\mathcal{H}\mathbf{M}^{-1/2} \end{array}\right.$$

Mass-weighted coordinates

Mass-weighted Hessian

$$\begin{aligned} \ddot{\mathbf{q}} &= -\mathbf{M}^{-1/2}\mathcal{H}\mathbf{M}^{-1/2}\mathbf{q} \\ &= -\mathbf{H}\mathbf{q} \end{aligned}$$

$$\left\{\begin{array}{l} \mathbf{q}(t) = \mathbf{q}\mathrm{e}^{-i\omega t} \\ \ddot{\mathbf{q}}(t) = -\omega^2\mathbf{q}(\mathrm{t}) \end{array}\right.$$

Oscillatory solution

$$\mathbf{H} = \mathbf{V}\boldsymbol{\Lambda}\tilde{\mathbf{V}}$$

$$\Lambda_{ij} = \omega_i^2\delta_{ij}$$

Goldstein, Ch. 10

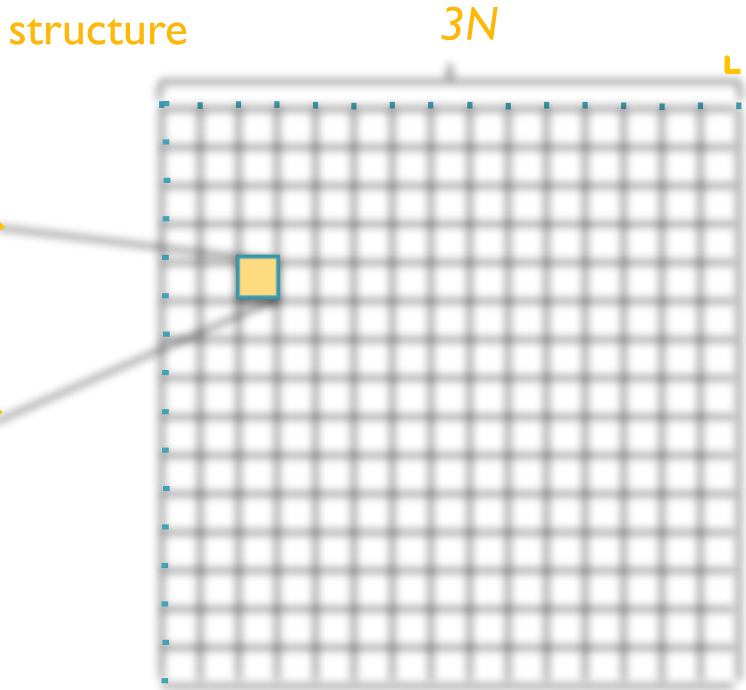
Anisotropic Network Model

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

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

Hessian is calculated directly from structure

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



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

Force constants

- Uniform within cutoff:

$$\gamma(\mathbf{r}_{ij}) = \begin{cases} \gamma & \left|\mathbf{r}_{ij}\right| < R_c \\ 0 \text{ } otherwise & \end{cases}$$

Tirion, PRL 77 (1996).
Bahar et al. Folding & Des 2 (1997).
Doruker et al. Proteins 40 (2000).

- Exponential decay:

$$\gamma(\mathbf{r}_{ij}) = \gamma_0 \exp\left(-\frac{\left|\mathbf{r}_{ij}\right|^2}{r_0^2} \right)$$

Hinsen et al. Proteins 33 (1998).

- Power law decay:

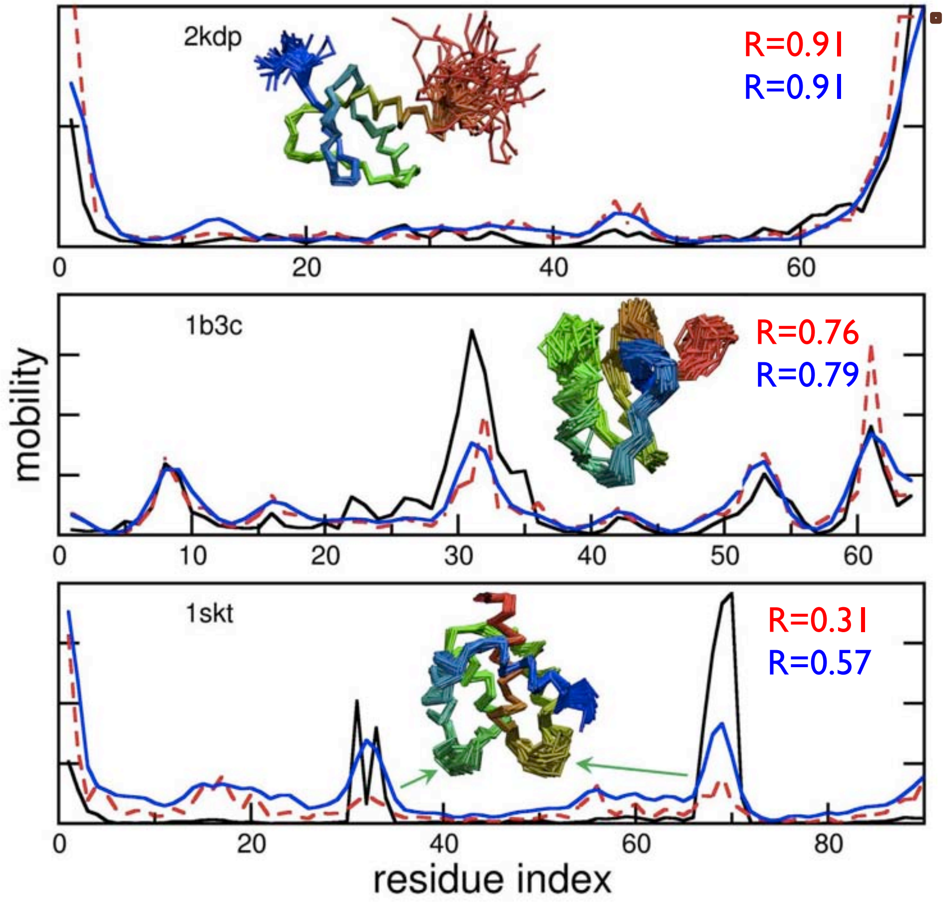
$$\gamma(\mathbf{r}_{ij}) = \begin{cases} c_0 + c_1\left|\mathbf{r}_{ij}\right| & \mathbf{r}_{ij} < R_0 \\ c_2\left|\mathbf{r}_{ij}\right|^{-6} & otherwise \end{cases}$$

Hinsen et al. Chem Phys 261 (2000).

$$\gamma(\mathbf{r}_{ij}) = \left|\mathbf{r}_{ij}\right|^{-2}$$

Yang et al. PNAS 106 (2009).

Force constants can be fine-tuned to improve agreement with data



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

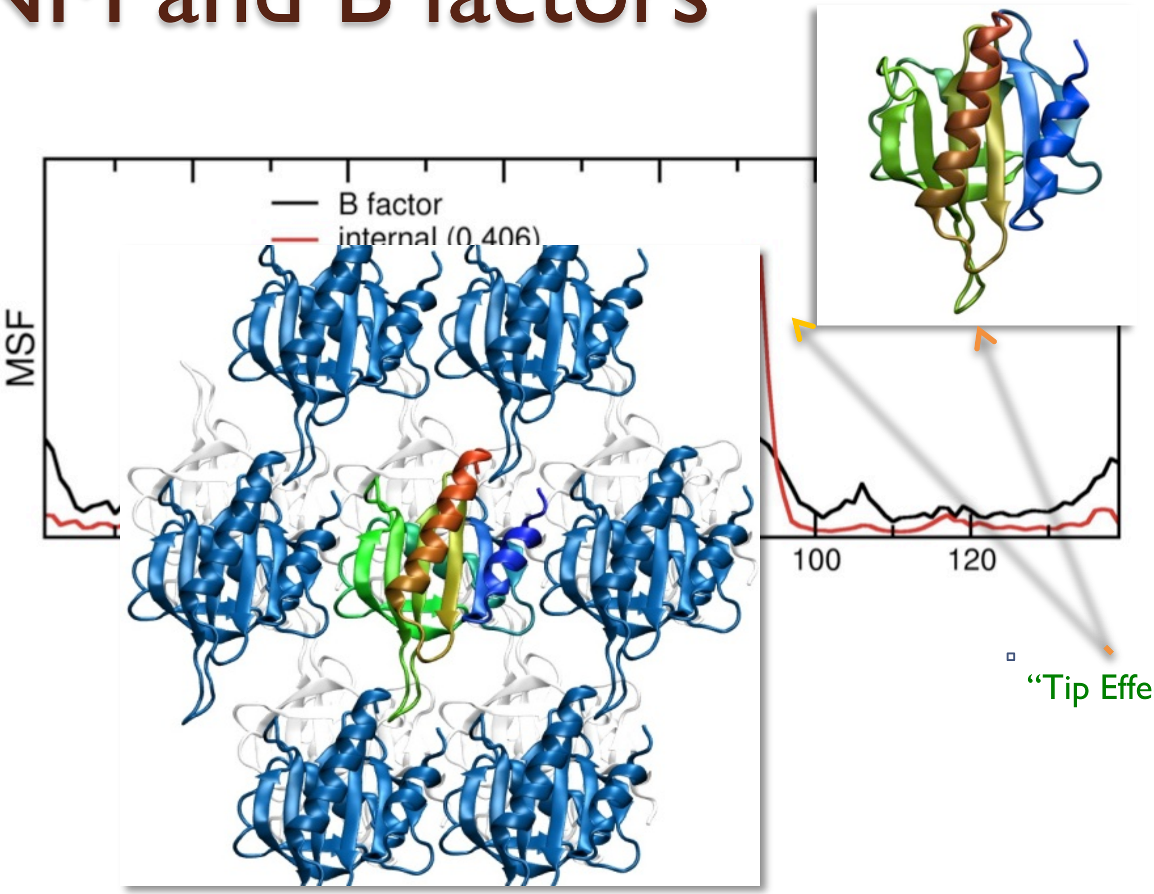
black: NMR
red: ENM
blue: modified ENM

GammaStructureBased()

ENM tutorial: Custom Gamma Functions

Lezon & Bahar. PLoS Comp Biol 6 (2010).

Improving correlation between ENM and B factors

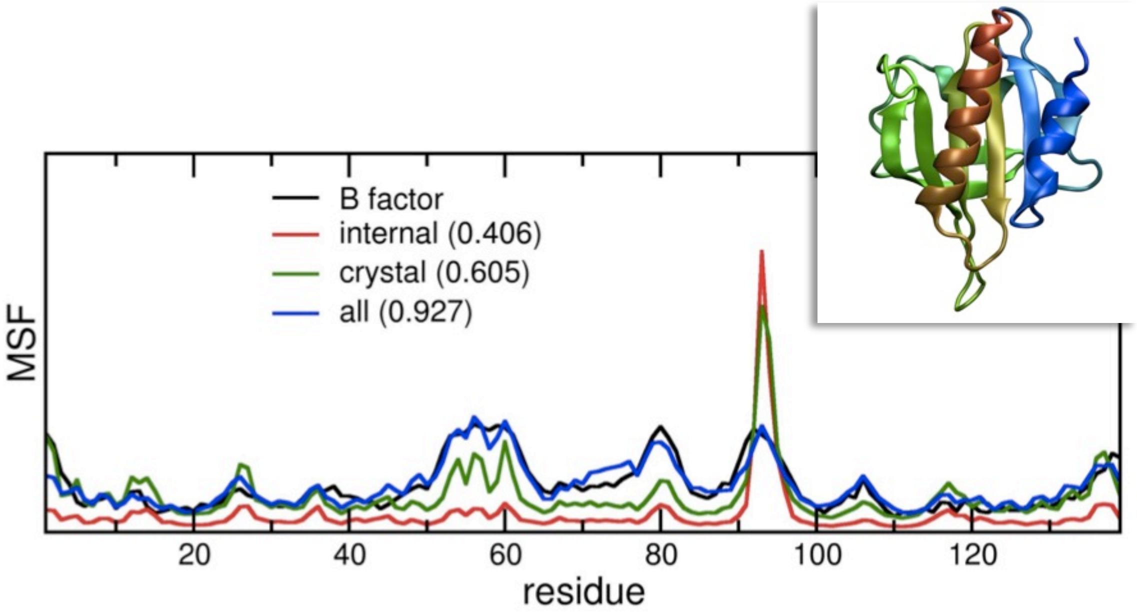


“Tip Effect”

Possible solution: Add crystal contacts

Lezon. Proteins 80 (2012).

Improving correlation between ENM and B factors

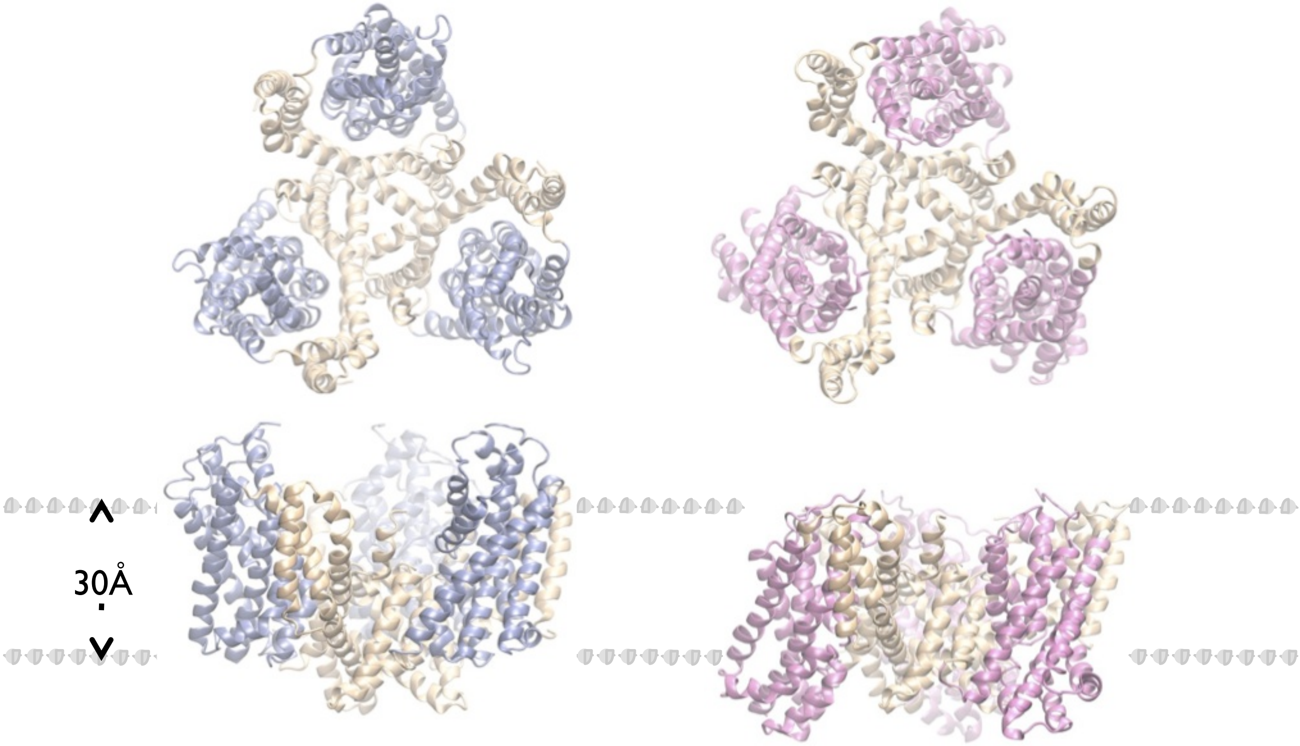


- Crystal contacts help, but do not eliminate tip effect.
  What about lattice vibrations?

`reduceModel()`

Lezon. Proteins 80 (2012).

Exploring structural transitions: Glutamate transporter

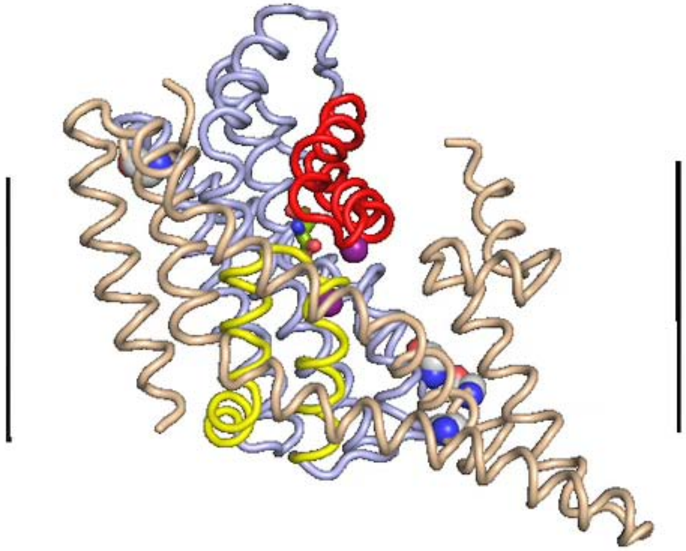


Outward Facing (OF)

Inward Facing (IF)

Exploring structural transitions: Glutamate transporter

Single subunit showing the transport domain moving across the membrane

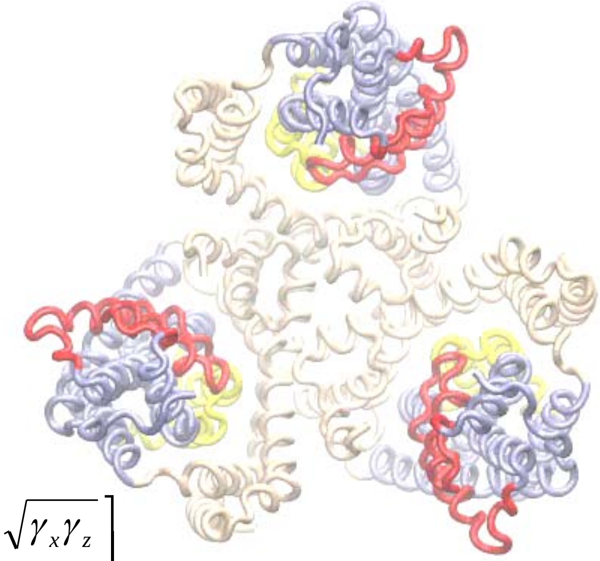


Reyes *et al.* Nature 462 (2009).

Exploring structural transitions: Glutamate transporter

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

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

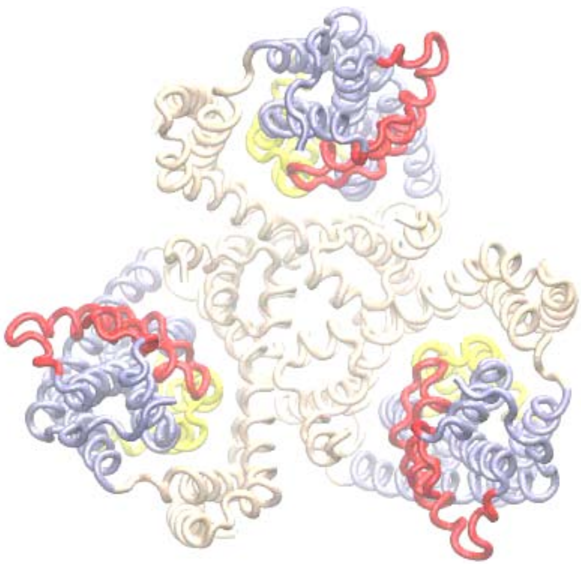


Altered radial force constants:

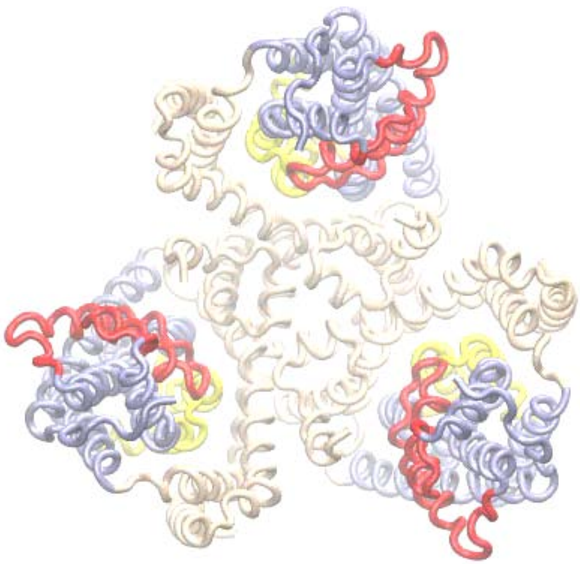
$$\mathbf{H_{ij}} = -\left(R_{ij}^{0}\right)^{-2}\begin{bmatrix} \left(x_{ij}^{0}\sqrt{\gamma_x}\right)^{2} & x_{ij}^{0}y_{ij}^{0}\sqrt{\gamma_x\gamma_y} & x_{ij}^{0}z_{ij}^{0}\sqrt{\gamma_x\gamma_z} \\ x_{ij}^{0}y_{ij}^{0}\sqrt{\gamma_x\gamma_y} & \left(y_{ij}^{0}\sqrt{\gamma_y}\right)^{2} & y_{ij}^{0}z_{ij}^{0}\sqrt{\gamma_y\gamma_z}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

Lezon & Bahar. Biophys J 102 (2012).

Exploring structural transitions: Glutamate transporter



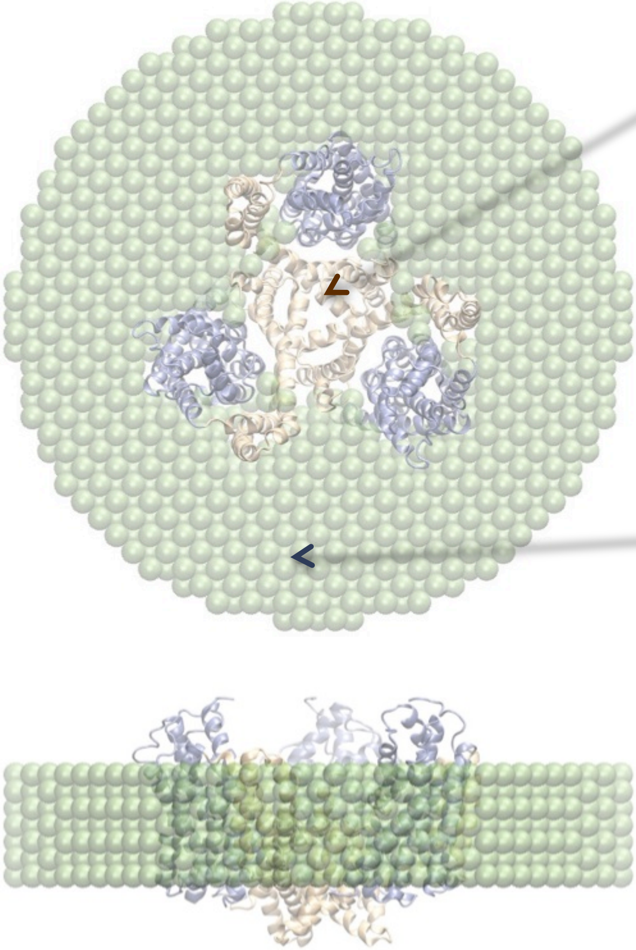
ANM: Large radial motions

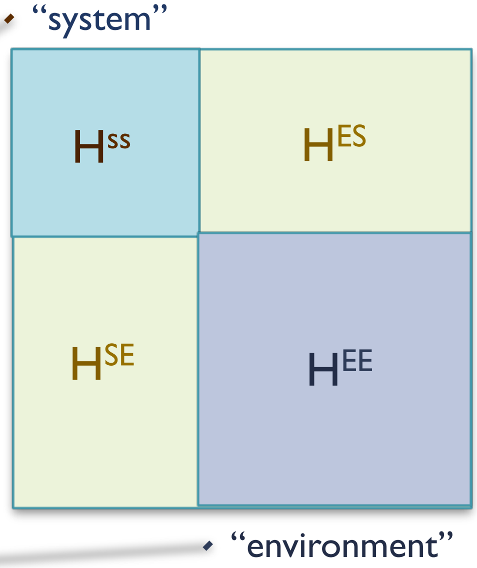


imANM

Lezon & Bahar. Biophys J 102 (2012).

Explicit membrane models





- "system"

$$\begin{array}{|c|c|} \hline H^{ss} & H^{ES} \\ \hline H^{SE} & H^{EE} \\ \hline \end{array}$$

- "environment"

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

$$V_{eff}\left(\mathbf{s}\right)=\tfrac{1}{2}\Delta\mathbf{s}^{T}\left(\mathbf{H}^{ss}{}'\right)\Delta\mathbf{s}$$

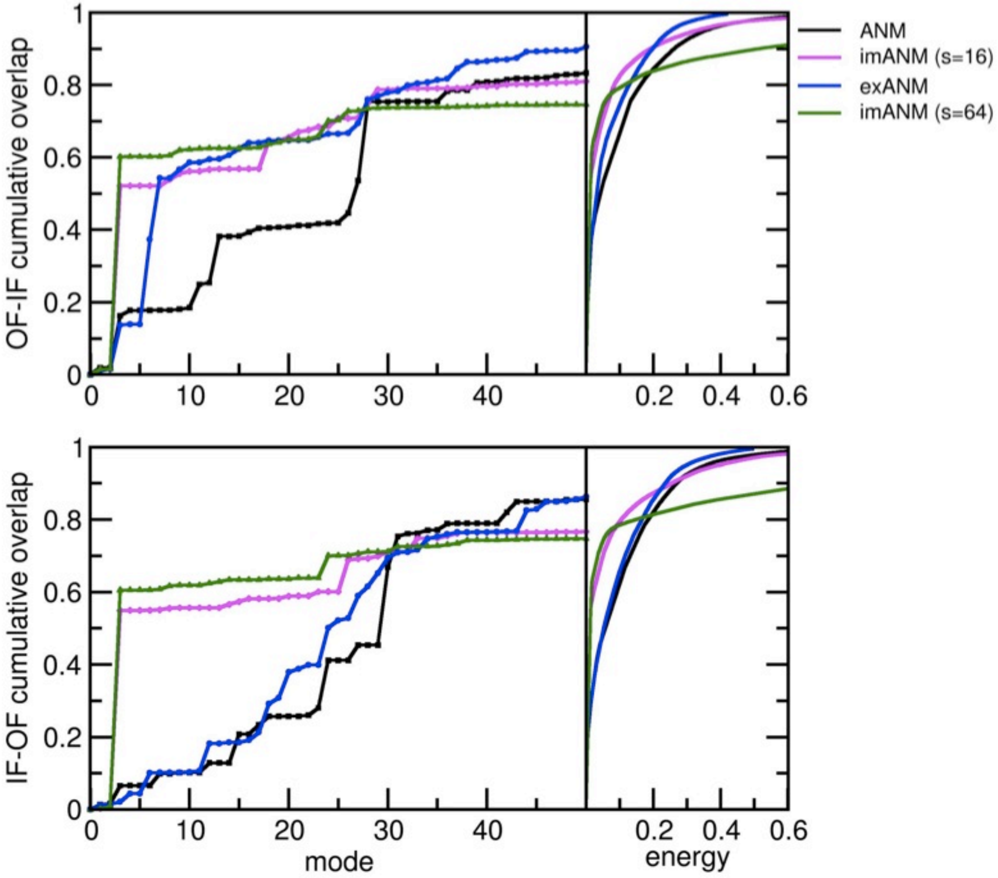
$$\mathbf{H}^{ss}{}'=\mathbf{H}^{ss}-\mathbf{H}^{SE}\left(\mathbf{H}^{EE}\right)^{-1}\mathbf{H}^{ES}$$

`reduceModel()`

Lezon & Bahar. Biophys J 102 (2012).

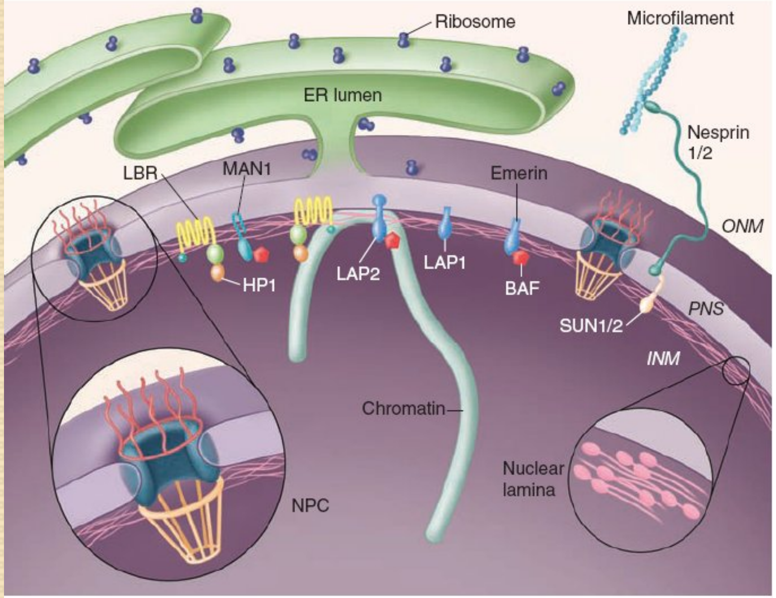
Ming & Wall. PRL 95 (2005).
Zheng & Brooks. Biophys J 89 (2005).

Exploring structural transitions: Glutamate transporter

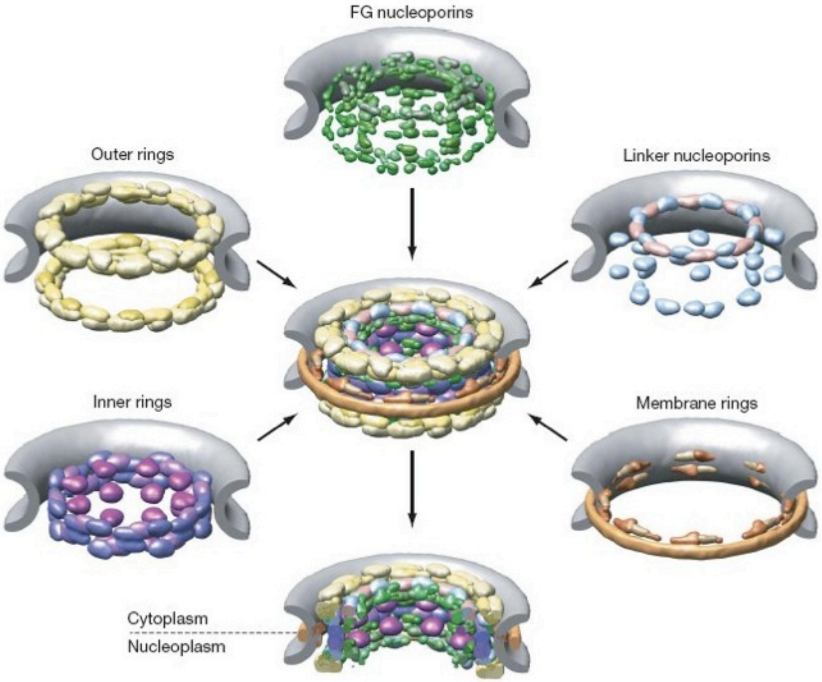


Lezon & Bahar. Biophys J 102 (2012).

Thinking bigger: The yeast nuclear pore complex



Stewart *et al.* Science 318 (2007).



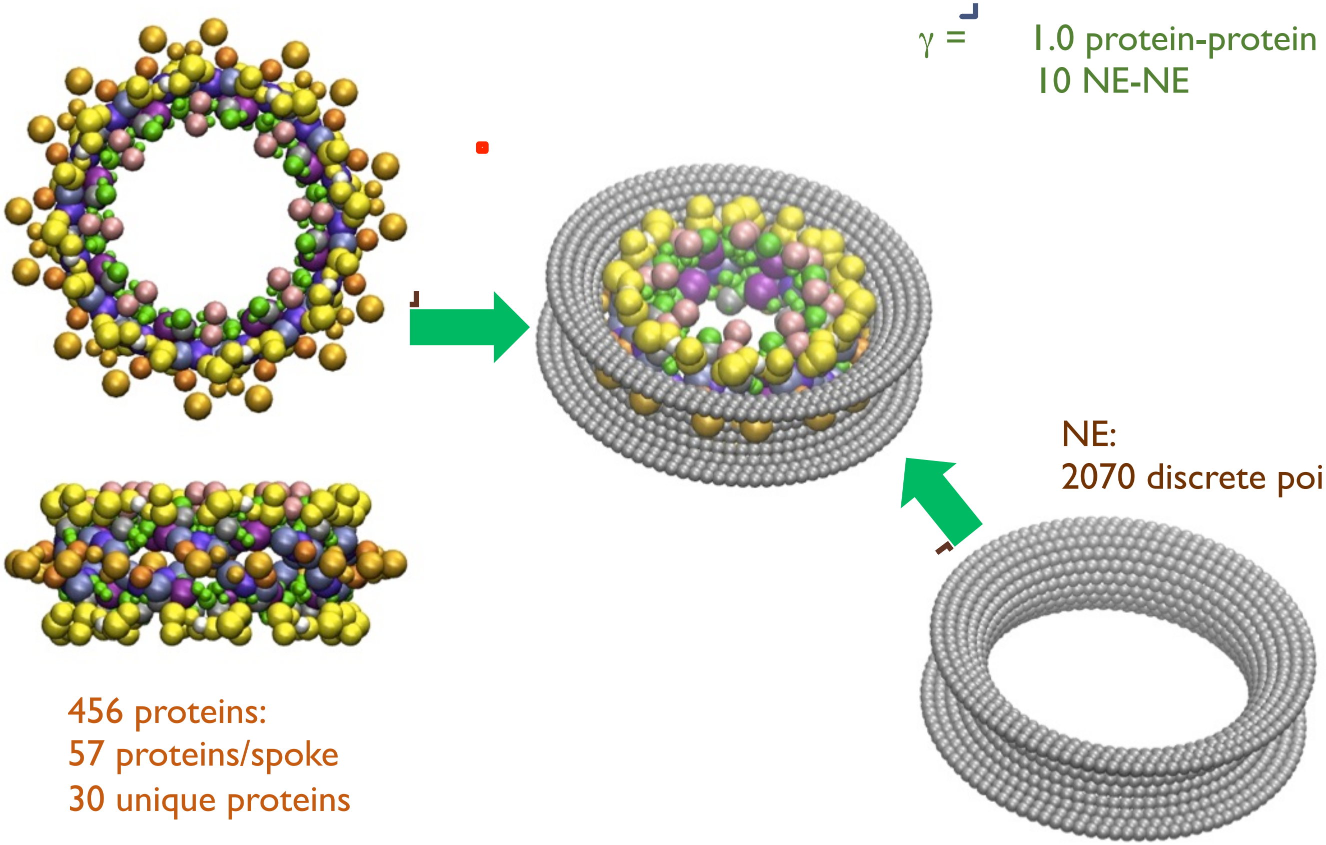
Alber *et al.* Nature 450 (2007).

ENM of NPC

R_c =
12nm protein-protein
8nm NE-NE
10nm protein-NE

γ =
1.0 protein-protein
10 NE-NE

NPC Model

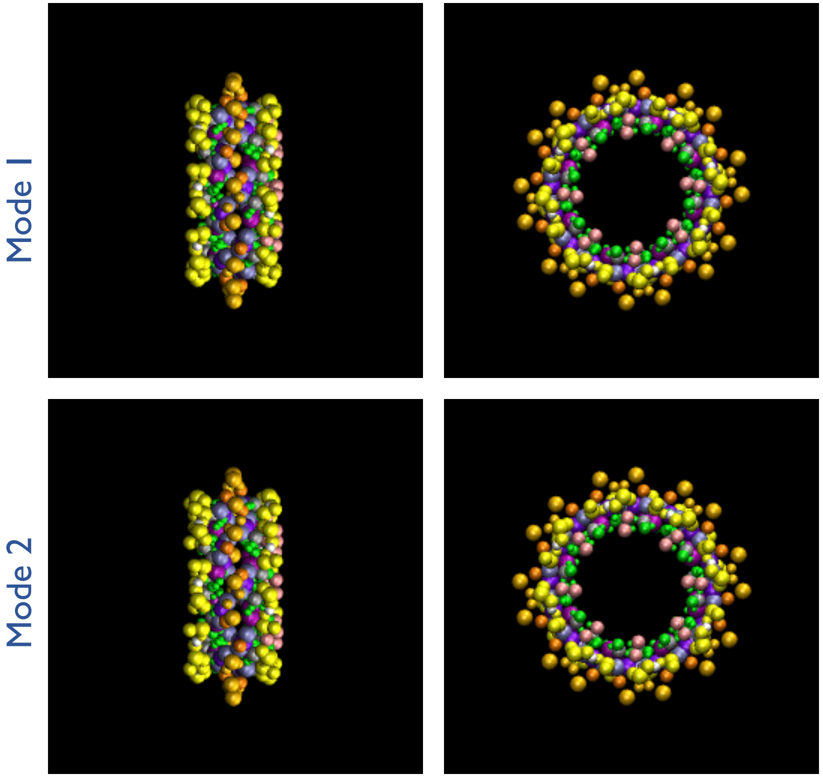


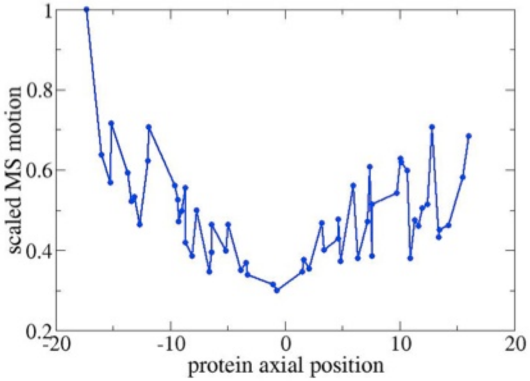
456 proteins:
57 proteins/spoke
30 unique proteins

NE:
2070 discrete points

Lezon *et al.* PLoS Comp Biol 5 (2009).

NPC slow modes

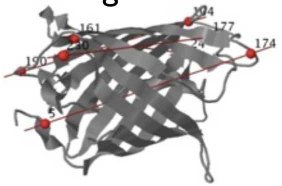




Lezon *et al*. PLoS Comp Biol 5 (2009).

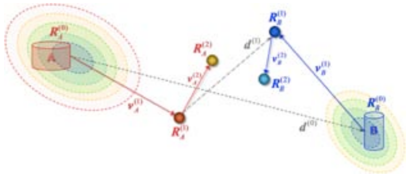
Other ENM applications

Pulling



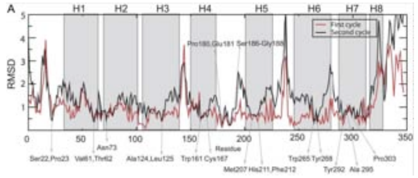
Eyal & Bahar (2008) *Biophys J* **94**:3424.

Transitions



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

Steered MD

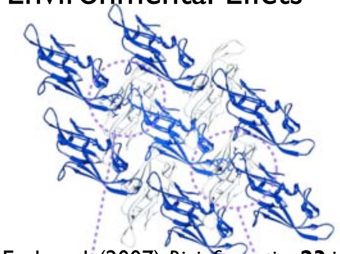


Isin et al. (2008) *Biophysical J* **95**:789.

Ensemble Analysis

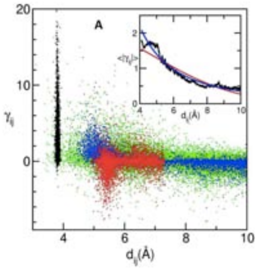
L-W Yang et al. (2009) *Bioinformatics* **25**: 606.
Bakan & Bahar (2009) *Proc Natl Acad Sci USA* **106**:14349.

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.