Supplementary Material

Initializing the EM Algorithm

As an initial estimate for $\boldsymbol{\delta}$, a uniform distribution is adopted. The kernel matrix $\boldsymbol{K}$ is conveniently constructed by diffusing $\boldsymbol{M}$ to a small number of iterations β to give $\boldsymbol{M}^{\beta}$ and selecting a small number of columns. In picking the columns of $\boldsymbol{M}^{\beta}$, a greedy decision is made. In particular, column i in $\boldsymbol{M}^{\beta}$ corresponds to information diffusion from residue v_i. The first kernel K_i that is picked corresponds to the residue v_i with the highest stationary probability π_i. Following the selection of K_i, all other residues j (and the corresponding columns K_j in $\boldsymbol{M}^{\beta}$) that fall within the half-height of the peak value of the probability distribution in K_i are eliminated from further consideration. This approach generates kernels that are spatially disjoint. The selection of kernels continues until every residue in the protein is within a half-height of the peak value of at least one kernel. While other kernel selection procedures are conceivable, we chose the greedy method for computational speed. In practice, we observed the EM algorithm generates results of biological interest that are insensitive to the initial estimates of $\boldsymbol{K}$ and $\boldsymbol{\delta}$.

Hierarchical Gaussian Network (hGNM) Algorithm

Here we present the methodology for generating **GNM** modes at different levels of coarse-graining the information on contact topology inherent to the network of residues, and reconstructing the detailed mode behavior by projecting the eigenvectors and eigenvalues generated at low levels of resolution back to their fine scale counterparts using the Markov chain propagation formalism, a method shortly referred to as hierarchical GNM (**hGNM**).

For **hGNM**, assume that the dimensions of the Kirchhoff matrices at the coarse, intermediate and fine scales are e, c and n respectively, where $e \leq c \ll n$. The affinity and Kirchhoff matrices at the coarsest level are not likely to be sparse, however a full eigen decomposition of the coarsest Kirchhoff matrix (size: $e \times e$) will be computationally the least expensive step. To reconstruct the eigen information at the fine-scale, assume we have access to the leading eigenvectors $\widetilde{\boldsymbol{U}}$ (size: $c \times e$) for $\widetilde{\boldsymbol{\Gamma}}$ (size: $c \times c$). Using this we generate the leading eigenvectors $\boldsymbol{U}$ (size: $n \times e$), and the leading eigenvalues $\boldsymbol{\Lambda} = \begin{bmatrix} \lambda_1 & \lambda_2 & \cdots & \lambda_e \end{bmatrix}$ (size: $e \times 1$) of the fine-scale Kirchhoff matrix $\boldsymbol{\Gamma}$ (size: $n \times n$). Let $\{\boldsymbol{U}_{\boldsymbol{\Gamma}}, \boldsymbol{\Lambda}_{\boldsymbol{\Gamma}}\}$ denote the eigenvectors and eigenvalues obtained from a direct decomposition of $\boldsymbol{\Gamma}$. There are several steps to the eigen reconstruction process:

1. The coarse-scale eigenvectors $\widetilde{\boldsymbol{U}}$ can be tranformed using the kernel matrix $\boldsymbol{K}$ to generate $\boldsymbol{U}$ as an approximation to $\boldsymbol{U}_{\boldsymbol{\Gamma}}$

$$\boldsymbol{U} = \boldsymbol{K}\widetilde{\boldsymbol{U}}.$$

2. This transformation alone is unlikely to set the directions of $\boldsymbol{U}$ exactly aligned with $\boldsymbol{U}_{\boldsymbol{\Gamma}}$. So, we update the directions in $\boldsymbol{U}$ by repeated application of the following iteration (called *power* iterations (Watkins, 2002): $\boldsymbol{U} \Leftarrow \boldsymbol{\Gamma_g U}$ Note, here instead of using $\boldsymbol{\Gamma}$ we use an adjusted matrix $\boldsymbol{\Gamma_g}$ given by $\boldsymbol{\Gamma}_g = \nu \boldsymbol{I} - \boldsymbol{\Gamma}$, where ν is a constant and $\boldsymbol{I}$ is an identity matrix. The power iterations will direct the eigenvectors to directions with large eigenvalues. But for fluctuation dynamics, we are interested in the *slow* eigen modes with *small* eigenvalues and hence an adjustment is made to the matrix $\boldsymbol{\Gamma}$. In particular, because of Gerschgorin theorem (Watkins, 2002) the eigenvalues of $\boldsymbol{\Gamma}$ are bound to lie in a disk centered around the origin with a radius ν that is no more than twice the largest element on the diagonal of $\boldsymbol{\Gamma}$.

3. Steps 1 and 2 need not preserve orthogonality of the eigenvectors in $\boldsymbol{U}$. We fix this by a Gram-Schmidt orthogonalization procedure (Watkins, 2002).

The eigenvalues are obtained from $\boldsymbol{\Lambda} = \text{diag}(\boldsymbol{U}^{\mathsf{T}} \boldsymbol{\Gamma}\, \boldsymbol{U})$. More details of this coarse to fine eigen mapping procedure are presented in Chennubhotla & Jepson (2005), including a discussion on the number of power iterations to use and setting appropriate thresholds for convergence. Next, we show **hGNM** maps structure-dynamics information between successive levels of the hierarchy with minimal loss in accuracy.

Table S1. **Summary of Intra- and Inter-Subunit Couplings and their Biological Implications**

Structural Element	**Predicted Role**	**Relevant Experimental Observation**	**Reference**
GroES loop E18–A33	Communication between GroES cap and *cis* ring; peaks at residues I25 and G24	Allosteric modulation of GroEL/substrate affinity and chaperonin cycle speed	Landry et al 1993 Shewmaker et al 2001
		Regulation of chaperonin and co-chaperonin interaction	e.g. Hohfeld et al 1994 Richardson et al 1994 Kovalenko et al 1994 Richardson et al 2001
		Transition from coil to β-hairpin upon GroEL binding; G24A mutant shows significant decrease in binding	Shewmaker et al 2004 Richardson et al 2001
V38–I49, A2-V6 and D523–P525 in *cis*; R36–K51 in *trans* ring	Intra-ring communication	Positive intra-ring cooperativity	See for example Yifrach et al 1995
E409–R501	Intra-ring communication	Intra-ring communication	Aharoni et al 1997
trans ring subunit K recruits short segments from subunit J; *cis* ring D from subunit E, i.e. they integrate their respective counterclockwise and clockwise neighbors	Information flow in opposite rotational directions in *cis* and *trans* rings	Negative cooperativity between the two rings Counter-rotations of two rings; a prominent mechanism of global motion	See for example Yifrach et al 1995 Saibil et al 2002
D179–L183, V381–K392, on *trans* ring I-domain coupled to adjacent subunit's A−domain (occurs exclusively in *trans* ring, not *cis* ring)	Enhanced stability of *trans* ring compared to *cis* ring, via inter-subunit A−I domains interactions	Salt bridge between E386 and R197 in the *trans* ring, which is broken in the ATP-bound (*cis*) form	Yifrach et al 1998 Braig et al 1994 White et al 1997 Ma et al 2000[1]
I333, D334, K321–V323, E214–S217 in *cis* ring, R350–E355, V128,E129 in *trans* ring, and E50–E53 in GroES	Act as GroEL hubs (cluster cores) for allosteric communication		
E461–V464, A109, K105, R452 in both *cis* and *trans*	Act as messengers in inter-ring allosteric communication	Mutant E461K causes disruption in inter-ring transfer of ATP-induced signal. R452, K105 form inter-ring salt-bridges with E461, E434 respectively.	Sewell et al 2004
T30–K34 in both *cis* and *trans* rings	Act as messengers in broadcasting information away from nucleotide-binding sites	L31–P33 coordinate the nucleotide (along with T90, G88, I493, T91, D495, G415, D87) in the X-ray structure	Xu et al 1997