Dissipative Electro-elastic Network Model of Protein Electrostatics

The statistical correlator between the displacements of residues i and j within the network surrounded by the thermodynamic bath at temperature T.
Some Results of ENM Compared to MD

- Network models are capable of reproducing the basic pattern of mean square displacements along the protein backbone.

- There is an overall underestimate of these displacement correlations compared to Molecular Dynamics (MD). Parameters can be varied to adjust the fit.
Adding Dissipation: Langevin Dynamics of Normal Modes

Instead of an elastic network of harmonic springs, we assume for each normal mode overdamped dynamics, with an external oscillatory force and a randomly fluctuating force – Langevin type dynamics.

\[
\int_0^t \zeta(t - t') \dot{q}_m(t') dt' + \lambda_m q_m = F(t) + R(t)
\]

\[
\chi_m(\omega) = \left[ i\omega \tilde{\xi}(\omega) + \lambda_m \right]^{-1}
\]

Elastic Response Function

\[
\chi_{\alpha\beta}^{\alpha\beta}(\omega) = C^{-1} \sum_m U_{m\alpha}^{\gamma\alpha} [\lambda_m + i\omega \tilde{\xi}(\omega)]^{-1} U_{m\beta}^{\gamma\beta}
\]

Displacement Response

\[
Re \left[ \chi_{ij}^{\alpha\beta}(0) \right] = \beta \left( \delta r_i^\alpha \delta r_j^\beta \right)
\]

Related to the dissipation within the network, the friction.
Two Debye Friction kernel

\[
\chi_m(\omega) = \left[ i\omega \tilde{\zeta}(\omega) + \lambda_m \right]^{-1}
\]

\[
\chi_m(\omega) = \frac{a}{i\omega \zeta_h + \lambda_m} + \frac{1 - a}{i\omega \zeta_l + \lambda_m}
\]
Adding Electrostatics

Displacements produce dipole moments

\[ \delta \mu_{ik}^m = q_{ik} \delta r_{im} \]

Creates change in electrostatic potential at the active site

\[ \delta \phi_0 = \sum_{m,i} \delta r_{im} \cdot E_{0i} \]
\[ E_{0i}^\alpha = \sum_k \frac{q_{ik}(r_0^\alpha - r_{ik}^\alpha)}{|r_0 - r_{ik}|^3} \]

In LRT, the displacements are caused by the force acting on residue i due residue j in response to the field perturbation produced by the probe charge placed at the active site.

\[ \delta r_{i}^\alpha(\omega) = \sum_j \chi_{ij}^{\alpha \beta}(\omega) \delta F_j^\beta(\omega) \quad \text{where} \quad \delta F_j(\omega) = -q_\omega E_{0j} \]

Finally, the response function connects the potential to the charge perturbation

\[ \delta \phi_0(\omega) = \chi_\phi(\omega) q_\omega \]

Electrostatic Potential Response

\[ \chi_\phi(\omega) = - \sum_{i,j} E_{0j}^\alpha \chi_{ij}^{\alpha \beta}(\omega) E_{0i}^\beta \]
Adding Electrostatics

Deformation of the protein matrix induced by the probe dipole results in an E-field at the active site due to the dipoles arising from the residue charges.

\[ E_0(\omega) = \sum_{ik} T_{ik} \cdot \delta \mu_{ik}(\omega) \]

Dipole tensor connects the position of the active site to the charge at residue i

The dipole moment at the atomic charge on the residue is caused by the displacement of that residue and can be written in terms of the displacement response function

\[ q_{ik} \delta r_i(\omega) = \delta \mu_{ik}(\omega) = q_{ik} \sum_j \chi_{ij}(\omega) \cdot \delta F_j(\omega) \]

with

\[ \delta F_j(\omega) = \sum_k q_{jk} T_{jk} \cdot \mathbf{m}_\omega \]

The proportionality between the perturbation and the response is the response function

\[ \chi^{\alpha\beta}_E(\omega) = \sum_{i,j,k,l} q_{ik} T^{\alpha\gamma}_{ik} \chi^\gamma_{ij}(\omega) T^{\delta\beta}_{jl} q_{jl} \]

\[ \chi_E(\omega) = \chi^{\alpha\alpha}_E(\omega) \]

\[ C_E(t) = \langle \delta \mathbf{E}(t) \cdot \delta \mathbf{E}(0) \rangle \]
Some Results of DENM compared to MD

Displacement Response

\[ C = 0.3 \text{ kcal/(mol Å}^2\text{)} < 1.0 \text{ kcal/(mol Å}^2\text{)} \]

Typically used to fit B-factors

The softening of the network is expected since ENMs cut the high frequency vibrations from the density of states.
Some Results of DENM compared to MD

Electrostatic Potential and Electric Field Response

\[ C = 0.6 \text{ kcal/(mol \(\AA^2\))} \]

The friction coefficient can be adjusted to reproduce the main loss peak in the electrostatic potential.

CytB → \(\zeta_l = 30\text{ns}\)

metMB → \(\zeta_l = 10\text{ns}\)

The parameters used to fit the electrostatic potential do not perform as well when applied to the electric field.
Adding Solvation of ionized residues

Hamiltonian Perturbation: \( H = E(R) - \sum_{i,j} E_{ij} \cdot m_j \)

Connects residue i with water dipole j

\[
\delta E_i \cdot m_j = \sum_k q_{ik} \delta r_i \cdot T_{ij} \cdot m_j
\]

Fluctuating water dipole

Only charged residues survive:

\[
\sum_k q_{ik} = q_i \neq 0
\]

After averaging over Gaussian fluctuations of water dipoles:

\[
F = \frac{(C/2)}{2} \sum_{i,j} \tilde{H}_{ij}^{\alpha\beta} \delta r_i^\alpha \delta r_j^\beta
\]

\[
\tilde{H}_{ij}^{\alpha\beta} = H_{ij}^{\alpha\beta} - C^{-1} \kappa_{ij}^{\alpha\beta} q_i q_j
\]

Solvation softening

\[
\kappa_{ij} = \tilde{T}_i(k) \ast \chi(k, k') \ast \tilde{T}_j(k')
\]

Connects position r in water with ith residue dipole

\[
\tilde{T}_i(k) = \int T(r - r_i) \theta(r) e^{ik \cdot r} d^3r
\]

Free energy of electro-elastic network
Solvation Terms

\[ \kappa_{ij}^{\mu\nu} = \frac{4y\alpha_i\alpha_j}{3} \left[ \frac{a(s, r)}{s^3} \delta_{\mu\nu}\delta_{ij} - (1 - \delta_{ij})b(s, r)T_{ij}^{\mu\nu} \right] \]

\[ \alpha_i = \frac{a_i}{(4\pi s^2)} \]

Ratio of the SASA to the total surface area of residue i

\[ a(s, r) = \delta_{r,0} + \frac{6s}{\pi} \int_0^\infty j_1^2(ks)j_0(kr)(S^L(k) - 1)dk \]

\[ b(s, r) = \theta(r - 2s) + \frac{6s}{\pi} \left( \frac{r}{s} \right)^3 \int_0^\infty j_1^2(ks)j_2(kr)(S^L(k) - 1)dk \]

1\textsuperscript{st} term represents solvation free energy of fluctuating dipole

2\textsuperscript{nd} term represents the water-mediated couplings of the dipolar fluctuations through the solvent polarization

The integrals are well represented by the structure factor at 0:

\[ a(s, r) = AS^L(0) \quad b(s, r) = S^L(0) \]

\[ S^L(0) = (3y)^{-1}(1 - \epsilon_s^{-1}) \quad A = 3.54 \quad s = 4.4\text{Å} \]
sDENM Hamiltonian

\[ \tilde{H}_{ij}^{\alpha\beta} = H_{ij}^{\alpha\beta} - C^{-1}\kappa_{ij}^{\alpha\beta} q_i q_j \]

\[ \kappa_{ij}^{\alpha\beta} = \frac{4\alpha_i \alpha_j}{9} \left( 1 - \frac{1}{\epsilon_s} \right) \left[ A(T, P) \frac{\delta_{\alpha\beta}\delta_{ij}}{s^3} - (1 - \delta_{ij}) T_{ij}^{\alpha\beta} \right] \]

dipole-dipole correlations of residue displacements
solvation of i

Dynamics

Two-Debye memory kernel:

\[ \chi_m(\omega) = \frac{a}{i\omega \zeta_h + \lambda_m} + \frac{1 - a}{i\omega \zeta_l + \lambda_m} \]

fitting parameters
Hessian eigenvalue

\[ \chi_{ij}^{\alpha\beta}(\omega) = C^{-1} \sum_m U_{mi}^{\gamma\alpha} \chi_m(\omega) U_{mj}^{\gamma\beta} \]

Response function: displacement of i due to an oscillatory force at j
Cytochrome B562 rmsd

Numbers indicate SASA scaled down to 45 Å²
CytB: potential response

\[ \chi_\phi(\omega) = -\sum_{i,j} E_{0j}^\alpha \chi_{ij}^{\alpha\beta}(\omega) E_{0i}^\beta \]
CytB: electric field response

\[ \chi_E^{\alpha\beta}(\omega) = \sum_{i,j,k,l} q_{ik} T_{ik}^{\alpha\gamma} \chi_{ij}^{\gamma\delta}(\omega) T_{jl}^{\delta\beta} q_{jl} \]

\[ \chi_E(\omega) = \chi_E^{\alpha\alpha}(\omega) \]

\[ \omega, \text{ ns}^{-1} \]
CytB: dielectric constant

\[ \chi_M(\omega) = \frac{1}{3} \sum_{ij} q_i q_j \chi^{\alpha\alpha}_{ij}(\omega) \]

New slow component
Nitrogen regulatory protein C (NtrC), NMR study by Kern and coworkers,

Allosteric displacement

Piezoelectric response:

$$\langle \delta r_i^\alpha(\omega) \rangle = -\sum_j \chi_{ij}^{\alpha\beta}(\omega) E_{j0}^\beta q_\omega$$

$$\delta r_i(\omega) = \left[ \langle \delta r_i^\alpha(\omega) \rangle \langle \delta r_i^\alpha(\omega) \rangle \right]^{1/2}$$

probe charge at the active site

$$q_\omega = 1$$

$$|\Delta q| = 2$$

ion charge

displacement between two structures, ion-free and ion-bound
“Picture” of allosteric effect

**Standard picture:**
Force perturbation propagates through the protein as elastic deformation.
Problem: elasticity is **non-specific**

**New picture:**
Response to electric stimulus propagates through highly-correlated \((1/r^3)\) net of ionized surface residues. Both the perturbation and response are non-local and surface-bound. Large free energy is stored in hydration and drives **amplification**.