

Supporting information for: Molecular Paradigms for Biological Mechanosensing

David Gomez,^{†,‡} Willmor J. Peña Ccoa,[‡] Yuvraj Singh,[‡] Enrique Rojas,[†] and
Glen M. Hocky^{*,‡}

[†]*Department of Biology, New York University, New York, NY 10003*

[‡]*Department of Chemistry, New York University, New York, NY 10003*

E-mail: hockyg@nyu.edu

Simple derivation of linear response result

In Eq. 2, we can replace $Q(X)$ with $\delta Q(X)$ by multiplying the top and bottom by $e^{-\beta F Q_0(X)}$, and then compute the average of δQ itself using Eq. 3, which gives

$$\langle \delta Q \rangle_F = \frac{\int dX \delta Q(X) e^{-\beta U(X) + \beta F \delta Q(X)}}{\int dX e^{-\beta U(X) + \beta F \delta Q(X)}}. \quad (\text{S1})$$

We can multiply the top and bottom by Z_0^{-1} , where $Z_0 = \int dX e^{-\beta U(X)}$. Note in the following that $\langle \delta Q(X) \rangle_0 = 0$ and $\langle (\delta Q(X))^2 \rangle_0 \equiv \sigma_Q^2$

Expanding the exponential for small $\beta F \delta Q(X)$ gives,

$$\langle \delta Q \rangle_F = \frac{\int dX \delta Q(X) e^{-\beta U(X)} (1 + \beta F \delta Q(X) + \frac{1}{2} (\beta F \delta Q(X))^2 + \dots)}{\int dX e^{-\beta U(X)} (1 + \beta F \delta Q(X) + \frac{1}{2} (\beta F \delta Q(X))^2 + \dots)} \quad (\text{S2})$$

$$= \frac{\langle \delta Q \rangle_0 + \beta F \langle \delta Q(X) \delta Q(X) \rangle_0 + \frac{1}{2} (\beta F)^2 \langle Q(X) (\delta Q(X))^2 \rangle_0 + \dots}{\langle 1 \rangle_0 + \beta F \langle \delta Q(X) \rangle_0 + \frac{1}{2} (\beta F)^2 \langle (\delta Q(X))^2 \rangle_0 + \dots} \quad (\text{S3})$$

$$= \beta F \sigma_Q^2, \quad (\text{S4})$$

where the last term follows from neglecting all terms $O(F^2)$, resulting in Eq. 4,

$$\langle \delta Q \rangle_F = \langle Q - \langle Q \rangle_0 \rangle_F = \beta F \sigma_Q^2. \quad (\text{S5})$$

We can also ask what the effect of a force along vector Q is on another quantity $\delta Q'(X) = Q'(X) - \langle Q'(X) \rangle_0$. In exactly analogous fashion, we arrive at equation Eq. 6,

$$\langle \delta Q' \rangle_F = \beta F \langle \delta Q'(X) \delta Q(X) \rangle_0 \equiv \beta F \text{Cov}(Q', Q) \quad (\text{S6})$$

Similar results have been derived before, for example in Ref. 1.

Effect of force on equilibrium constants

The equilibrium constant in a two state system is given by $K_{eq} = P(R)/P(L)$, where L and R are the left and right states in a two-state model, as in Fig. 3.

The probability of being in a state A can be defined using a characteristic function²

$$\chi_A(\vec{X}) = \begin{cases} 1 & \vec{X} \in A \\ 0 & \text{otherwise} \end{cases}$$

The probability of being in a state A is given by

$$P(A) = \langle \chi_A \rangle = \frac{\int d\vec{X} \chi_A(\vec{X}) e^{-\beta U(\vec{X})}}{\int d\vec{X} e^{-\beta U(\vec{X})}} \quad (\text{S7})$$

For the 1D problem in Fig. 3, this simplifies to

$$P(A) = \langle \chi_A \rangle = \frac{\int dQ \chi_A(Q) e^{-\beta U(Q)}}{\int dQ e^{-\beta U(Q)}} \quad (\text{S8})$$

We can take a very strict definition of state R and L such that the system is only in the state if Q is precisely at the minimum. In this case, we can define the characteristic functions $\chi_R = \delta(Q - Q_R)$ and $\chi_L = \delta(Q - Q_L)$, with δ the Dirac delta function.

With this definition,

$$K_{eq} = \frac{P(R)}{P(L)} = \frac{\int dQ \delta(Q - Q_R) e^{-\beta U(Q)}}{\int dQ \delta(Q - Q_L) e^{-\beta U(Q)}} = \frac{e^{-\beta U(Q_R)}}{e^{-\beta U(Q_L)}} = e^{-\beta(U(Q_R) - U(Q_L))} \quad (\text{S9})$$

The Helmholtz free energy of a state A is given by $F(A) = -k_B T \ln(P(A))$, and so the difference in free-energies between the states at constant temperature is given by

$$\Delta F = F(R) - F(L) = -k_B T \ln \left(\frac{P(R)}{P(L)} \right) = -k_B T \ln K_{eq} = U(Q_R) - U(Q_L). \quad (\text{S10})$$

The fact that the free energy difference is equal to the energy difference is reflective of the fact that we are considering only a one-dimensional problem.

Simulation details

MD simulations in Fig. 1 and Fig. 2 were performed in Gromacs³ at $T = 300K$ with a timestep of $dt = 2\text{fs}$. Lysozyme was started from the PDB structure 1AKI using the CHARMM36 forcefield,⁴ solvated in TIP3P water, and neutralized with chloride ions. Production MD was performed with the Parrinello-Rahman barostat and the v-rescale ther-

mostat. Data was taken from 60 to 110 ns of simulation time. HP35 was started from the PDB structure 1YRF and prepared for simulation using CHARMM-GUI⁵ using the CHARMM36m forcefield with TIP3P water,⁶ and was neutralized and ionized with 50 mMol KCl. Production MD was performed with the Parrinello-Rahman barostat and Nose-Hoover thermostat. Data was taken from times 550ns to 600ns of production MD. Open structures in Fig. 8B were taken from preliminary simulations using Plumed⁷ with an applied 200pN constant force for the intermediate structure, and a simulation at 500K run with FISST⁸ for the fully extended structure. Trp-cage simulations were started from the PDB structure 2JOF and solvated in TIP3P water, using the Amber99SB*-ILDN forcefield.^{9,10} Production MD was performed with the Parrinello-Rahman barostat and the v-rescale thermostat. MD data was taken from the final 50ns of a 1 microsecond MD simulation.

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