Extending a Spectrin Repeat Unit I. Linear Force-Extension Response

Supplemental Material

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NEMD Force

This section elaborates on the derivation of the NEMD force discussed in the text. In this work, a thermodynamic force is defined as the partial derivative of the free energy under isothermal conditions,

$$F_0(L) = -\left(\frac{\partial A}{\partial L}\right)_T, \tag{1}$$

where A is the free energy, L is the length of the simulation cell in the z direction, T is the temperature, and the zero subscript signifies that the system is at equilibrium (or in the quasi-static limit). An effective spring constant for the spectrin repeat unit can be obtained by measuring the relationship between the force and extension, as described in more detail in the main text.

Here, an expression for the derivative of Eq. 1 that can easily be measured using the NEMD simulations will be constructed. The final result,

$$F_0(L) = \lim_{\omega \to 0} \langle P_{zz} V \rangle / L, \tag{2}$$

is intuitively obvious: the force is just the pressure in the z direction multiplied by the cross-sectional area of the box. But the left-hand side of Eq. 2 is a thermodynamic quantity defined by Eq. 1, whereas the right-hand side of Eq. 2 is obtained from the atomistic-level simulations. There are a number of equivalent ways to derive Eq. 2. In this section, two derivations are discussed in order to highlight the formal link between thermodynamic properties of the system and the atomistic-level dynamics.

To begin, consider the dissipation function (1, 2),

$$\Omega(\mathbf{\Gamma}) = \beta \dot{H}(\mathbf{\Gamma}) - \Lambda(\mathbf{\Gamma}). \tag{3}$$

In this equation, $\mathbf{\Gamma} \equiv (\mathbf{r}^N, \mathbf{p}^N, \mathscr{A})$ is the phase space vector, indicating the location of the trajectory in phase space at a particular time t, where $\mathbf{r}^N \equiv (\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N)$, and $\mathscr{A}$ is the cross-sectional area. The specific case where $P_{xx} = P_{yy} = 0$ is considered, where no work is done in the x and y directions. This aspect is reflected in the form of the dissipation function. The instantaneous energy, or Hamiltonian, of the system is,

$$H(\mathbf{\Gamma}) = \sum_i \frac{\mathbf{p}_i}{m_i} + \Phi(\mathbf{r}^N), \tag{4}$$

where $\Phi(\mathbf{r}^N)$ is the potential energy of the system. The phase space compression factor $\Lambda(\mathbf{\Gamma})$ is given by the Liouville equation (3),

$$\frac{\mathrm{d} \ln f(\mathbf{\Gamma})}{\mathrm{d}t} = -\Lambda(\mathbf{\Gamma}), \tag{5}$$

where $f(\mathbf{\Gamma})$ is the distribution function, or the probability of observing the system at a particular point in phase space. The dissipation function, Eq. 3, can be directly related to the reversible derivative of the free energy, as will be shown below. For the remainder of this discussion, the problem will be restricted to the NEMD equations of motion employed in the main text.

To show how the dissipation function is related to the free energy, consider the ensemble average of the dissipation function divided by $\dot{L}$,

$$k_{\mathrm{B}} T \langle \Omega(\mathbf{\Gamma}) \rangle / \dot{L} = \langle \dot{H}(\mathbf{\Gamma}) \rangle / \dot{L} - k_{\mathrm{B}} T \langle \Lambda(\mathbf{\Gamma}) \rangle / \dot{L}. \tag{6}$$

The thermodynamic internal energy, U, is just the ensemble average of the Hamiltonian,

$$\left(\frac{\partial U}{\partial L} \right)_T = \langle \dot{H}(\mathbf{\Gamma}) \rangle / \dot{L}, \tag{7}$$

where the chain rule has been used to convert the partial derivative with respect to length into time derivatives. Now define a new function,

$$\mathscr{S} = -k_{\mathrm{B}}\langle \ln f(\mathbf{\Gamma})\rangle. \tag{8}$$

It can be shown (4) that, at equilibrium, this function is equal to the entropy, or $S = \lim_{\omega\to 0}\mathscr{S}$. Taking the derivative of $\mathscr{S}$ reveals,

$$\left(\frac{\partial \mathscr{S}}{\partial L}\right)_T = k_{\mathrm{B}}\langle \Lambda(\mathbf{\Gamma})\rangle/\dot{L}, \tag{9}$$

where a chain rule has again been used. Substituting Eqs. 7 and 9 into Eq. 6 and taking the quasi-static limit gives,

$$\lim_{\omega\to 0} k_{\mathrm{B}}T\langle \Omega(\mathbf{\Gamma})\rangle/\dot{L} = \left(\frac{\partial U}{\partial L}\right)_T - T\left(\frac{\partial S}{\partial L}\right)_T. \tag{10}$$

With the free energy defined as $A = U - TS$, it is easily recognized that,

$$\left(\frac{\partial A}{\partial L}\right)_T = \lim_{\omega\to 0} k_{\mathrm{B}}T\langle \Omega(\mathbf{\Gamma})\rangle/\dot{L}. \tag{11}$$

Equation 11 represents the formal relationship between the dissipation function and the thermodynamic properties of the system. The remainder of this discussion will be concerned with deriving the expression for the dissipation function in terms of the equations of motion.

As described in the text, the NEMD equations of motion used in this particular study are,

$$\dot{\mathbf{\Gamma}} \equiv \begin{cases} \dot{\mathbf{r}}_i &= \dfrac{\mathbf{p}_i}{m_i} + \dot{\phi}(r_{x_i}\hat{\mathbf{i}} + r_{y_i}\hat{\mathbf{j}}) + \dot{\epsilon} r_{z_i}\hat{\mathbf{k}} \\ \dot{\mathbf{p}}_i &= \mathbf{F}_i - \dot{\phi}(p_{x_i}\hat{\mathbf{i}} + p_{y_i}\hat{\mathbf{j}}) - \dot{\epsilon} p_{z_i}\hat{\mathbf{k}} - \alpha\mathbf{p}_i \\ \dot{\mathscr{A}} &= 2\dot{\phi}\mathscr{A} \end{cases}. \tag{12}$$

The thermostat multiplier α maintains a constant temperature by instantaneously adding or removing heat from the system. The barostat term $\dot{\phi}$ maintains, on average, constant pressure in the x and y directions (so that $P = \langle \frac{1}{2}(P_{xx}+P_{yy})\rangle = 0$), and $\dot{\epsilon}$ is the predetermined strain rate in the z direction which drives changes in the length L of the simulation cell. The form of these equations of motion could be used to generate a constant NPT ensemble at equilibrium (with the volume V substituted for the area $\mathscr{A}$). However, in the case that $P = 0$ (i.e., no work is done in the x and y directions), these equations of motion can also be employed to evaluate Eq. 11, as will be shown.

The equations of motion employed in this study can be used to find explicit expression for the time derivative of the Hamiltonian and phase space compression factor which appear in the equation for the dissipation function, Eq. 3. The time derivative of the Hamiltonian is,

$$\begin{aligned} \dot{H}(\mathbf{\Gamma}) &= \left(\frac{\mathrm{d}H(\mathbf{\Gamma})}{\mathrm{d}\mathbf{\Gamma}}\right) \cdot \left(\frac{\mathrm{d}\mathbf{\Gamma}}{\mathrm{d}t}\right), & (13) \\ &= \sum_i \left[\frac{\mathbf{p}_i}{m_i} \cdot \dot{\mathbf{p}}_i - \mathbf{F}_i \cdot \dot{\mathbf{q}}_i\right]. & (14) \end{aligned}$$

Substituting in the equations of motion gives,

$$\dot{H}(\mathbf{\Gamma}) = -\dot{\phi}\left[\sum_i \frac{p_{x_i}^2 + p_{y_i}^2}{m_i} + F_{x_i} r_{x_i} + F_{y_i} r_{y_i}\right] - \dot{\epsilon}\left[\sum_i \frac{p_{z_i}^2}{m_i} + F_{z_i} r_{z_i}\right] - \alpha \sum_i \frac{\mathbf{p}_i^2}{m_i}. \quad (15)$$

The expressions for the instantaneous pressure tensor and kinetic temperature can be identified (5), giving,

$$\dot{H}(\mathbf{\Gamma}) = -(P_{xx} + P_{yy}) V \dot{\phi} - P_{zz} V \dot{\epsilon} - 3N k_{\mathrm{B}} T_k \alpha. \quad (16)$$

The phase space compression factor is (3),

$$\Lambda(\mathbf{\Gamma}) = \frac{\partial}{\partial \mathbf{\Gamma}} \cdot \dot{\mathbf{\Gamma}}, \quad (17)$$

which under these dynamics is given by,

$$\begin{aligned} \Lambda(\mathbf{\Gamma}) &= \frac{\partial}{\partial \mathbf{r}} \cdot \dot{\mathbf{r}} + \frac{\partial}{\partial \mathbf{p}} \cdot \dot{\mathbf{p}} + \frac{\partial}{\partial B} \dot{B}, & (18) \\ &= -3N\alpha + 2\dot{\phi}. & (19) \end{aligned}$$

Note that the $-3N\alpha$ term is extensive, whereas the $2\dot{\phi}$ term is intensive and thus will not contribute to $\Lambda(\mathbf{\Gamma})$ in the thermodynamic, or large N, limit (and the simulations verify this approximation).

Substituting Eqs. 16 and 19 into the equation for the dissipation function, Eq. 3, gives,

$$k_{\mathrm{B}}T\Omega(\mathbf{\Gamma}) = -(P_{xx}+P_{yy})V\dot{\phi} - P_{zz}V\dot{\epsilon} - 3Nk_{\mathrm{B}}T_k\alpha + 3Nk_{\mathrm{B}}T\alpha. \tag{20}$$

Taking the ensemble average of the dissipation function gives,

$$k_{\mathrm{B}}T\langle\Omega(\mathbf{\Gamma})\rangle = -\langle P_{zz}V\rangle\dot{\epsilon}. \tag{21}$$

In deriving Eq. 21, two approximations have been made. In the thermodynamic (large N) limit, the instantaneous kinetic temperature approaches the temperature of the bath, so $\langle\alpha T_k\rangle \simeq \langle\alpha\rangle T$. Furthermore, since the x and y dimensions of the simulation cell are able to fluctuate under zero stress (and thus can do no work), the terms involving P_{xx} and P_{yy} will on average be zero. The simulations verified that these conditions were met and that Eq. 21 is valid. Equation 21 can also be written as,

$$k_{\mathrm{B}}T\langle\Omega(\mathbf{\Gamma})\rangle/\dot{L} = -\langle P_{zz}V\rangle/L. \tag{22}$$

Substitution of this equation into Eq. 11 gives,

$$\left(\frac{\partial A}{\partial L}\right)_T = -\lim_{\omega\to 0}\langle P_{zz}V\rangle/L, \tag{23}$$

which, in turn, gives the final expression for force, Eq. 2.

An alternative way to derive Eq. 2 makes use of the simple thermodynamic identity relating isothermal changes in the free energy to constant entropy changes in the internal energy,

$$\left(\frac{\partial A}{\partial L}\right)_T = \left(\frac{\partial U}{\partial L}\right)_S. \tag{24}$$

The chain rule can again be used to convert derivatives with respect to length into derivatives with respect to time,

$$F_0(L) = -\left(\frac{\partial\langle H\rangle}{\partial t}\right)_S\left(\frac{\partial t}{\partial L}\right)_S. \tag{25}$$

In the zero frequency or equilibrium limit ($\omega \to 0$), the constant entropy derivative is equal to the adiabatic derivative. The adiabatic derivative of H is identical to Eq. 16, except that under adiabatic conditions no heat is exchanged and thus $\alpha = 0$. Substituting these results into Eq. 25 gives Eq. 2. Note that while Eq. 25 used the adiabatic time derivative, it is not necessary that the equations of motion actually be propagated under adiabatic conditions. The *total* derivative (as opposed to the *partial* derivative) of U involves both adiabatic and isometric contributions (6),

$$\mathrm{d}U = \left(\frac{\partial U}{\partial V}\right)_S \mathrm{d}V + \left(\frac{\partial U}{\partial S}\right)_V \mathrm{d}S. \tag{26}$$

So even though the system is propagated under constant temperature equations of motion, the adiabatic partial derivative of the internal energy still exists and is a well-defined quantity that can be expressed in terms of the equations of motion.

As a final note, Eq. 2 motivates the definition of an instantaneous finite frequency force,

$$F_\omega = \langle P_{zz} V \rangle / L. \tag{27}$$

This force can be shown to be equal to the derivative of the work, which can include irreversible contributions. The first law of thermodynamics can be written as,

$$\dot{U} = \dot{W} + \dot{Q}, \tag{28}$$

where W is the work done on the system, U is the internal energy of the system, and Q is the heat transferred to the system. Comparing Eq. 28 with the ensemble average of Eq. 16 reveals,

$$\begin{aligned} \dot{W} &= -\langle P_{zz} V \rangle \dot{\epsilon}, & (29) \\ \dot{Q} &= -3Nk_{\mathrm{B}} \langle T_k \alpha \rangle. & (30) \end{aligned}$$

Using the chain rule again it is found that,

$$F_\omega = -\frac{\mathrm{d}W}{\mathrm{d}L}. \tag{31}$$

Subsequently, the dissipation function can be considered to be the time derivative of the irreversible work.

References

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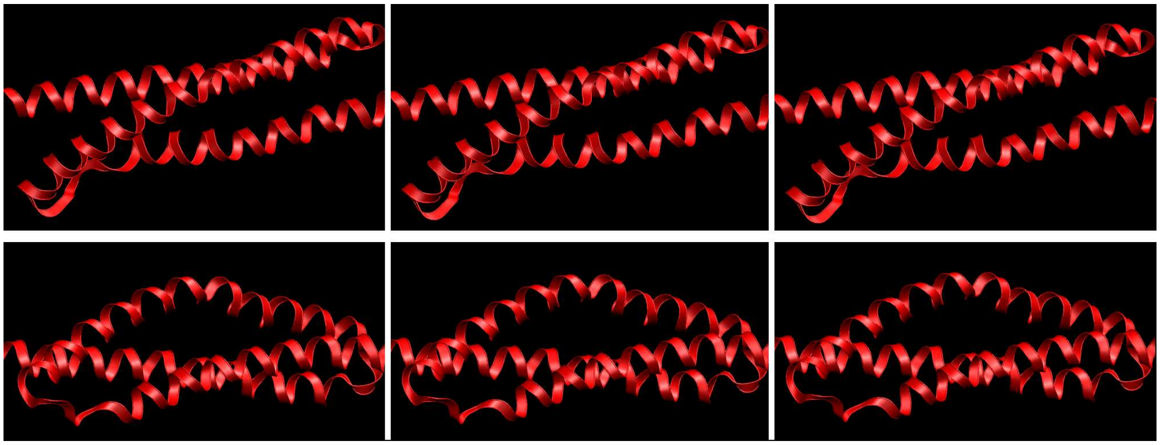
Figure 1: This figure shows two views of three periodic images of the spectrin repeat unit studied using cyclic expansion NEMD. The C terminus is on the left and the N terminus is on the right. The bottom figure shows that the linker must incur a slight bend in order to connect with its image. Note that since all forces are calculated based on the minimum image convention (5), the position of the "edges" of the periodic cell are inconsequential.



S. Paramore et al., Figure 1