Supporting Information for

A Generalized Transition State Theory Treatment of Water-Assisted Proton Transport Processes in Proteins

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1. Derivation of Transition State Rate Constant in Terms of an n-Dimensional PMF

The general expression of the rate constant when assuming the dividing surface of an N-dimensional PMF is defined as $\xi_1 = c$, is given by

$$k_{TST} = \frac{1}{Q^R}\int \frac{d\mathbf{q}\, d\mathbf{p}_q}{h^{3N}} \int d\boldsymbol{\xi} \int d\mathbf{p}_{\boldsymbol{\xi}}\, \delta(\xi_1 - c) e^{-\beta H}\, \Theta(\dot{\xi}_1)\dot{\xi}_1 \tag{S1}$$

Here, $\boldsymbol{\xi} = (\xi)_i$ is the CV vector with dimension *n*, and ξ_1 is the PT CV related to the excess proton CEC., while $\mathbf{p}_\xi$ is the conjugate momentum vector of $\boldsymbol{\xi}$.

The Hamiltonian of the system can be expressed as a function of the $\boldsymbol{\xi}$ and $\mathbf{p}_\xi$ vectors as

$$H = \frac{1}{2}\mathbf{p}_\xi^T \mathbf{Z}_\xi \mathbf{p}_\xi + \frac{1}{2}\mathbf{p}_q^T \mathbf{Z}_q \mathbf{p}_q + V(\boldsymbol{\xi}, \mathbf{q}) \tag{S2}$$

where $\mathbf{Z}_\xi$ and $\mathbf{Z}_q$ are the mass matrices for the CVs from the degrees of freedom. The definition of $\mathbf{Z}_\xi$ is given by Eq. (3).

The rate expression now becomes

$$k_{TST} = \frac{1}{Q^R}\int \frac{d\mathbf{q}\, d\mathbf{p}_q}{h^{3N}} \int d\boldsymbol{\xi}\ \delta(\xi_1 - c) e^{-\beta(\frac{1}{2}\mathbf{p}_q^T \mathbf{Z}_q \mathbf{p}_q + V(\boldsymbol{\xi},\mathbf{q}))} \int d\mathbf{p}_\xi\ \Theta(\dot{\xi}_1)\dot{\xi}_1 e^{-\beta\frac{1}{2}\mathbf{p}_\xi^T \mathbf{Z}_\xi \mathbf{p}_\xi} \tag{S3}$$

Note that by incorporating

$$\dot{\boldsymbol{\xi}} = \frac{\partial H}{\partial \mathbf{p}_\xi} = \mathbf{Z}_\xi \mathbf{p}_\xi \tag{S4}$$

one can transform the representation from $\mathbf{p}_\xi$ to $\dot{\boldsymbol{\xi}}$,

The transition matrix $\mathbf{A}_\xi$ is the inverse matrix of $\mathbf{Z}_\xi$, and is expressed in the following form

$$\mathbf{A}_n = \mathbf{Z}_\xi^{-1} = \begin{pmatrix} a & \mathbf{b}^T \\ \mathbf{b} & \mathbf{A}_{n-1} \end{pmatrix} \tag{S5}$$

The kinetic term in the exponential now becomes

$$\frac{1}{2}\mathbf{p}_\xi^{\mathbf{T}} \mathbf{Z}_\xi \mathbf{p}_\xi = \frac{1}{2}\dot{\boldsymbol{\xi}}^{\mathbf{T}} \mathbf{Z}_\xi^{-\mathbf{1}} \dot{\boldsymbol{\xi}} \tag{S6}$$

From Eq. (S4), (S5) and (S6), we have

$$\int d\mathbf{p}_\xi\ \Theta(\dot{\xi}_1)\dot{\xi}_1 e^{-\beta\frac{1}{2}\mathbf{p}_\xi^T \mathbf{Z}_\xi \mathbf{p}_\xi} = |\mathbf{A}_\xi| \int d\dot{\xi}_n \ldots \int d\dot{\xi}_2 \int_0^\infty d\dot{\xi}_1\, \dot{\xi}_1 e^{-\frac{\beta}{2}\dot{\boldsymbol{\xi}}^T \mathbf{Z}_\xi^{-1} \dot{\boldsymbol{\xi}}} \tag{S7}$$

Using the Gaussian integral formula,

$$\int dx_n \ldots \int dx_2 \int_0^\infty dx_1 x_1 \exp -\frac{1}{2}\left(\mathbf{x}^T A \mathbf{x}\right) = \left(\sqrt{2\pi}\right)^{n-1} \frac{\sqrt{|\mathbf{A}_{n-1}|}}{|\mathbf{A}_n|} \tag{S8}$$

the integration over the velocity representation in Eq. (S7) becomes

$$\int d\mathbf{p}_\xi\ \Theta(\dot{\xi}_1)\dot{\xi}_1 e^{-\beta\frac{1}{2}\mathbf{p}_\xi^T \mathbf{Z}_\xi \mathbf{p}_\xi} = |\mathbf{A}_n| \left(\sqrt{2\pi}\right)^{n-1} \frac{\sqrt{\beta^{n-1}|\mathbf{A}_{n-1}|}}{\beta^n |\mathbf{A}_n|} \tag{S9}$$

$$= \left(\sqrt{\frac{2\pi}{\beta}}\right)^{n-1} \frac{1}{\beta}\sqrt{|\mathbf{A}_{n-1}|}$$

By then incorporating the Gaussian formula

$$\int d\mathbf{p}_\xi \;\; e^{-\beta\frac{1}{2}\mathbf{p}_\xi^T\mathbf{Z}_\xi\mathbf{p}_\xi} = \sqrt{\frac{(2\pi)^n|\mathbf{A}_n|}{\beta^n}} \tag{S10}$$

the integral over the momentum on the left-hand side of Eq. (S8) can be expressed as

$$\begin{aligned}\int d\mathbf{p}_\xi \;\; \Theta(\dot{\xi}_1)\dot{\xi}_1 \, e^{-\beta\frac{1}{2}\mathbf{p}_\xi^T\mathbf{Z}_\xi\mathbf{p}_\xi} &= \frac{\left(\sqrt{\frac{2\pi}{\beta}}\right)^{n-1}\frac{1}{\beta}\sqrt{\beta^n}\sqrt{|\mathbf{A}_{n-1}|}}{\left(\sqrt{2\pi}\right)^n\sqrt{|\mathbf{A}_n|}}\int d\mathbf{p}_\xi \;\; e^{-\beta\frac{1}{2}\mathbf{p}_\xi^T\mathbf{Z}_\xi\mathbf{p}_\xi} \\ &= \frac{1}{\sqrt{2\pi\beta}}\frac{\sqrt{|\mathbf{A}_{n-1}|}}{\sqrt{|\mathbf{A}_n|}}\int d\mathbf{p}_\xi \;\; e^{-\beta\frac{1}{2}\mathbf{p}_\xi^T\mathbf{Z}_\xi\mathbf{p}_\xi}\end{aligned} \tag{S11}$$

By applying the inverse operator on both sides of Eq. (S5)

$$\mathbf{Z}_\xi = \mathbf{A}_n^{-1} \tag{S12}$$

and due to the fact that the specific element in an inverse matrix can be explicitly expressed with the matrix

$$(\mathbf{Z}_\xi)_{11} = \mathbf{Z}_{11} = \frac{|\mathbf{A}_{n-1}|}{|\mathbf{A}_n|} \tag{S13}$$

we can substitute the integrand to obtain the same integration results in the rate expression as

$$\begin{aligned}k_{TST} &= \frac{1}{Q^R}\int\frac{d\mathbf{q}\,d\mathbf{p}_q}{h^{3N}}\int d\boldsymbol{\xi}\;\;\delta(\xi_1 \\ &\qquad - c)e^{-\beta(\frac{1}{2}\mathbf{p}_\xi^T\mathbf{Z}_\xi\mathbf{p}_\xi+V(\boldsymbol{\xi},\mathbf{q}))}\frac{1}{\sqrt{2\pi\beta}}\sqrt{Z_{11}}\int d\mathbf{p}_\xi \;\; e^{-\beta\frac{1}{2}\mathbf{p}_\xi^T\mathbf{Z}_\xi\mathbf{p}_\xi} \\ &= \frac{1}{Q^R\sqrt{2\pi\beta}}\int\frac{d\mathbf{q}\,d\mathbf{p}_q d\boldsymbol{\xi} d\mathbf{p}_\xi}{h^{3N}}\;\;\delta(\xi_1 - c)\sqrt{Z_{11}}e^{-\beta H} \\ &= \frac{1}{Q^R\sqrt{2\pi\beta}}\frac{\int\frac{d\mathbf{q}\,d\mathbf{p}_q d\boldsymbol{\xi} d\mathbf{p}_\xi}{h^{3N}}\;\;\delta(\xi_1 - c)\sqrt{Z_{11}}e^{-\beta H}}{\int\frac{d\mathbf{q}\,d\mathbf{p}_q d\boldsymbol{\xi} d\mathbf{p}_\xi}{h^{3N}}\;\;\delta(\xi_1 - c)e^{-\beta H}} \\ &\qquad \times\int\frac{d\mathbf{q}\,d\mathbf{p}_q d\boldsymbol{\xi} d\mathbf{p}_\xi}{h^{3N}}\;\;\delta(\xi_1 - c)e^{-\beta H} \\ &= \frac{1}{Q^R\sqrt{2\pi\beta}}\left\langle\sqrt{Z_{11}}\right\rangle_{\xi_1=c}\int\frac{d\mathbf{q}\,d\mathbf{p}_q d\boldsymbol{\xi} d\mathbf{p}_\xi}{h^{3N}}\;\;\delta(\xi_1 - c)\,e^{-\beta H} \\ &= \frac{1}{\sqrt{2\pi\beta}}\left\langle\sqrt{Z_{11}}\right\rangle_{\xi_1=c}\frac{\int d\boldsymbol{\xi}\, e^{-\beta W(\xi_1=c)}}{Q^R}\end{aligned} \tag{S14}$$

where $Z_{11} = \sum_{k=1}^{3N}\frac{1}{M_k}\left(\frac{\partial\xi_1}{\partial r_k}\right)^2$ is the inverse value of the effective mass of the first CV.

2. Calculation of the ensemble average of $\langle\sqrt{\mathbf{Z}_\xi}\rangle$ among transition states in terms of a 2D PMF

1) Review of WHAM scheme to obtain a 1D PMF for the transition ridge $\xi_1 = c$ in the 2D PMF

First, let us review WHAM. WHAM here attempts to maximize the likelihood of probability summing over window k and bin i of ξ_2 axis at transition ridge $\xi_1 = c$.

Statement 1:

Minimize $-\ln L_{WHAM} = -\sum_k \sum_i \ln\left(\pi_i^k\right)^{N_i^k} = -\sum_k \sum_i N_i^k \ln\left(f^k \gamma_i^k \pi_i\right)$ so that $\sum_i \pi_i = 1$.

Here, $\pi_i = P(\xi_2 = (\xi_2)_i \mid \xi_1 = c)$ is the conditional probability of ξ_2 falling into bin i out of whole transition ridge $\xi_1 = c$. π_i^k is the biased probability at simulation condition k that falls into bin i. π_i and π_i^k are related by the known umbrella potential added, shown as $\pi_i^k = f^k \gamma_i^k \pi_i$. Here, γ_i^k is the constant bias factor caused by adding umbrella window k.$\gamma_i^k = e^{-\kappa\left((\xi_2)_i - (\mathrm{center}^k)\right)^2}$. $f^k = \frac{1}{\sum_l \pi_l \gamma_l^k}$ is the normalization factor that ensures $\sum_i \pi_i^k = 1$.

Statement 2:

$$\max_{v}\left[\min_{\pi_i}\left(-\ln L_{\mathrm{WHAM}} + v * \left(\sum_i \pi_i - 1\right)\right)\right]$$

Statement 1 is equal to statement 2 due to Lagrange Duality theory.

To solve $\min_{\pi_i}(-\ln L_{\mathrm{WHAM}} + v \cdot (\sum_i \pi_i - 1))$, we do derivative over π_i for all possible i.

$$\frac{\partial}{\partial \pi_i}\left(-\sum_k \sum_j N_j^k \ln\left(\frac{\gamma_j^k \pi_j}{\sum_l \pi_l \gamma_l^k}\right) + v \cdot \left(\sum_j \pi_j - 1\right)\right) = 0 \quad \forall\, i \tag{S15}$$

$$\frac{\partial}{\partial \pi_i}\left(-\sum_k \sum_j \left[N_j^k \cdot \ln \gamma_j^k \pi_j - N_j^k \cdot \ln \sum_l \pi_l \gamma_l^k\right] + v \cdot \sum_j \pi_j - v\right) = 0 \quad \forall\, i \tag{S16}$$

$$-\sum_k \frac{N_i^k}{\pi_i} + \sum_k\left(\left(\sum_j N_j^k\right) \cdot \frac{\gamma_i^k}{\sum_l \pi_l \gamma_l^k}\right) + v = 0 \quad \forall\, i \tag{S17}$$

$$v = \frac{1}{\pi_i}\sum_k N_i^k - \sum_k\left(\left(\sum_j N_j^k\right) \cdot \gamma_i^k f^k\right) \tag{S18}$$

This equation stands for all π_i. Then we need to get v that maximize the following expression

$$\max_{v}\left[-\sum_{k}\sum_{j} N_j^k \ln\left(\frac{\gamma_j^k \pi_j}{\sum_l \pi_l \gamma_l^k}\right) + v\cdot\left(\sum_j \pi_j - 1\right)\right] \tag{S19}$$

It's obvious to get that $v = 0$. The solution is shown below,

$$\pi_i = \frac{\sum_k N_i^k}{\sum_k\left(\left(\sum_j N_j^k\right)\cdot \gamma_i^k f^k\right)} \qquad f^k = \frac{1}{\sum_l \pi_l \gamma_l^k} \tag{S20}$$

2) Calculation of $\langle \mathrm{A}\rangle_{\xi_1=c}$ on the 2D-PMF

Now we want to calculate the ensemble average for $\langle A\rangle_{\xi_1=c}$, where the physical quantity happens to be $\sqrt{Z_{\xi_{11}}}$.

$$\langle A\rangle_{\xi_1=c} = \sum_i\left(P(\xi_2 = (\xi_2)_i \mid \xi_1 = \mathrm{c})\cdot \langle A\rangle_{i,\xi_1=\mathrm{c}}\right) \tag{S21}$$

Here, $P(\xi_2 = (\xi_2)_i \mid \xi_1 = \mathrm{c}) = \pi_i = \frac{e^{-\beta E_i}}{\sum_j e^{-\beta E_j}} = \frac{\sum_k N_i^k}{\sum_k\left(\left(\sum_j N_j^k\right)\cdot\gamma_i^k f^k\right)}$.

Notice that $\langle A\rangle_i^l$(unbiased) is the unbiased, reweighted ensemble average derived from quantity A sampled at window l and falls into bin i, $\langle A\rangle_i^l$(biased) is the biased ensemble average of quantity A directly sampled at window l and falls into bin i

$$\langle A\rangle_{i,\xi_1=\mathrm{c}} = \sum_l\left(w_{il}\cdot\langle A\rangle_i^l(\text{unbiased})\right) \tag{S22}$$

$$\langle A\rangle_i^l(\text{unbiased}) = \frac{\sum_t A_i^j(t)e^{+\beta V_i^l(t)}}{\sum_t e^{+\beta V_i^l(t)}} = \frac{\int \mathrm{d}\xi_1\int \mathrm{d}\xi_2\int \mathrm{d}\boldsymbol{r}^{3N-2} A_i^j(t)e^{-\beta\left(\mathrm{H}+V_i^j\right)}e^{+\beta V_i^j}}{\int \mathrm{d}\xi_1\int \mathrm{d}\xi_2\int \mathrm{d}\boldsymbol{r}^{3N-2} e^{-\beta\left(\mathrm{H}+V_i^j\right)}e^{+\beta V_i^j}} \tag{S23}$$

$$\langle A\rangle_i^l(\text{biased}) = \frac{1}{T}\sum_t A_i^j(t) = \frac{\int \mathrm{d}\xi_1\int \mathrm{d}\xi_2\int \mathrm{d}\boldsymbol{r}^{3N-2} A_i^j(t)e^{-\beta\left(\mathrm{H}+V_i^j\right)}}{\int \mathrm{d}\xi_1\int \mathrm{d}\xi_2\int \mathrm{d}\,\boldsymbol{r}^{3N-2} e^{-\beta\left(\mathrm{H}+V_i^j\right)}} \tag{S24}$$

Since $V_i^l(t)$ is a time-independent potential, we have

$$\langle A\rangle_i^l(\text{unbiased}) = \langle A\rangle_i^l(\text{biased}) \tag{S25}$$

Hence,

$$\langle A\rangle_{i,\xi_1=\mathrm{c}} = \sum_l\left(w_{il}\cdot\langle A\rangle_i^l(\text{unbiased})\right) = \sum_l\left(w_{il}\cdot\frac{1}{T}\sum_t A_i^l(t)\right) \tag{S26}$$

To solve w_l , we look at the probability of bin i and its decomposition to the probability of this bin contributing from window l.

$$\pi_i = \sum_l\left(w_{il}\cdot\pi_i^l(\text{unbiased})\right) = \sum_l\left(w_{il}\cdot\frac{\frac{N_i^l}{\gamma_i^l}}{\sum_j\frac{N_j^l}{\gamma_j^l}}\right) \tag{S27}$$

From WHAM derivation in the first section, we know that

$$\pi_i = \frac{\sum_l N_i^l}{\sum_k \left(\left(\sum_j N_j^k\right) \cdot \gamma_i^k f^k \right)} = \sum_l \frac{N_i^l}{\sum_k \left(\left(\sum_j N_j^k\right) \cdot \gamma_i^k f^k \right)} \tag{S28}$$

Hence,

$$w_{il} \cdot \frac{\frac{N_i^l}{\gamma_i^l}}{\sum_j \frac{N_j^l}{\gamma_j^l}} = \frac{N_i^l}{\sum_k \left(\left(\sum_j N_j^k\right) \cdot \gamma_i^k f^k \right)} \tag{S29}$$

$$w_{il} = \frac{\gamma_i^l \cdot \sum_j \frac{N_j^l}{\gamma_j^l}}{\sum_k \left(\left(\sum_j N_j^k\right) \cdot \gamma_i^k f^k \right)} = \frac{\pi_i}{\sum_l N_i^l} \cdot \gamma_i^l \cdot \sum_j \frac{N_j^l}{\gamma_j^l} \tag{S30}$$

To sum up,

$$\begin{aligned} \left\langle \sqrt{Z_\xi} \right\rangle_{\xi_1 = \mathrm{c}} &= \sum_i \left(P(\xi_2 = (\xi_2)_i \mid \xi_1 = \mathrm{c}) \cdot \langle A \rangle_{i, \xi_1 = \mathrm{c}} \right) \\ &= \sum_i \left(\pi_i \cdot \sum_l \left(w_{il} \cdot \frac{1}{T} \sum_t A_i^l(t) \right) \right) \\ &= \sum_i \left[\frac{\pi_i^2}{\sum_l N_i^l} \cdot \sum_l \left(\gamma_i^l \cdot \left(\sum_j \frac{N_j^l}{\gamma_j^l} \right) \cdot \frac{1}{T} \sum_t \left(\sqrt{Z_\xi} \right)_i^l (t) \right) \right] \end{aligned} \tag{S31}$$

3) Calculation of $\sqrt{\mathbf{Z}_\xi}$ on a Given Frame of the Trajectory

The inverse value of effective mass of ξ is defined as

$$Z_\xi \coloneqq \sum_{i=1}^{3N} \frac{1}{M_i} \left(\frac{\partial \xi}{\partial r_i} \right)^2 \tag{S32}$$

where N is the number of atoms in the system, M_i is the mass of atom i, r_i is the Cartesian coordinate (either x, or y, or z dimension) of atom i.

$$\frac{\partial \xi}{\partial r_i} = \left(\frac{\partial \xi}{\partial V_{\mathrm{bias}}} \right) \left(\frac{\partial V_{\mathrm{bias}}}{\partial r_i} \right) \tag{S33}$$

Since

$$\frac{\partial \xi}{\partial V_{\mathrm{bias}}} = -\left(\frac{\partial V_{\mathrm{bias}}(\xi)}{\partial \xi} \right)^{-1} = -\left(\frac{\partial \left[\frac{1}{2} \kappa (\xi - s)^2 \right]}{\partial \xi} \right)^{-1} = -\frac{1}{\kappa(\xi - s)} \tag{S34}$$

$$\frac{\partial V_{\mathrm{bias}}}{\partial r_i} = -F_{r_i}^{\mathrm{bias}} \tag{S35}$$

$F_{r_i}^{\mathrm{bias}}$, the bias force on each atom along r_i direction, is provided by PUMED package, dump-force command.

So, we have

$$\frac{\partial \xi}{\partial r_i} = \left(\frac{\partial \xi}{\partial V_{\text{bias}}}\right)\left(\frac{\partial V_{\text{bias}}}{\partial r_i}\right) = \frac{F_{r_i}^{\text{bias}}}{\kappa(\zeta - s)} \tag{S36}$$

$$Z_\xi = \sum_{i=1}^{3N} \frac{1}{M_i}\left(\frac{\partial \xi}{\partial r_i}\right)^2 = \sum_{i=1}^{3N} \frac{1}{M_i}\left(\frac{F_{r_i}^{\text{bias}}}{\kappa(\xi - s)}\right)^2 \tag{S37}$$

$$\sqrt{Z_\xi} = \sqrt{\sum_{i=1}^{3N} \frac{1}{M_i}\left(\frac{F_{r_i}^{\text{bias}}}{\kappa(\xi - s)}\right)^2} \tag{S38}$$

3. The Proof of equipartition theorem $\langle \mathbf{Z}_{11} \rangle = \beta\langle \dot{\xi}_1^2 \rangle$

$$\begin{aligned} \beta\langle \dot{\xi}_1^2 \rangle &= \int \frac{\mathrm{d}\mathbf{q}\,\mathrm{d}\mathbf{p}_\mathrm{q}}{\mathrm{h}^{3\mathrm{N}}} \int \mathrm{d}\boldsymbol{\xi}\ \beta\,\mathrm{e}^{-\beta(\frac{1}{2}\mathbf{p}_\mathrm{q}^\mathrm{T}\mathbf{Z}_\mathrm{q}\mathbf{p}_\mathrm{q} + \mathrm{V}(\boldsymbol{\xi},\mathbf{q}))} \int \mathrm{d}\mathbf{p}_\xi\, \dot{\xi}_1^2\, \mathrm{e}^{-\beta\frac{1}{2}\dot{\boldsymbol{\xi}}^\mathrm{T}\mathbf{Z}_\xi^{-1}\dot{\boldsymbol{\xi}}} \\ &= \int \frac{\mathrm{d}\mathbf{q}\,\mathrm{d}\mathbf{p}_\mathrm{q}}{\mathrm{h}^{3\mathrm{N}}} \int \mathrm{d}\boldsymbol{\xi}\ \beta\,\mathrm{e}^{-\beta\left(\frac{1}{2}\mathbf{p}_\mathrm{q}^\mathrm{T}\mathbf{Z}_\mathrm{q}\mathbf{p}_\mathrm{q} + \mathrm{V}(\boldsymbol{\xi},\mathbf{q})\right)} \int \mathrm{d}\dot{\boldsymbol{\xi}}\, |\mathbf{A}|\, \dot{\xi}_1^2\, \mathrm{e}^{-\beta\frac{1}{2}\dot{\boldsymbol{\xi}}^\mathrm{T}\mathbf{Z}_\xi^{-1}\dot{\boldsymbol{\xi}}} \\ &= \int \frac{\mathrm{d}\mathbf{q}}{\mathrm{h}^{3\mathrm{N}}} \int \mathrm{d}\boldsymbol{\xi}\ \ \mathrm{e}^{-\beta\mathrm{V}(\boldsymbol{\xi},\mathbf{q})} \sqrt{\frac{(2\pi)^n}{\beta|\mathbf{A}|}}\,|\mathbf{A}_{n-1}| \end{aligned} \tag{S39}$$

The last line of Eq. (S39) employs the integral formula

$$\int \mathrm{d}\mathbf{x}\,\mathrm{x}_1^2\,\mathrm{e}^{-\frac{\beta}{2}\mathbf{x}^\mathrm{T}\mathbf{A}\mathbf{x}} = \sqrt{\frac{(2\pi)^n}{\beta^3|\mathbf{A}|^3}}\,|\mathbf{A}_{n-1}| \tag{S40}$$

Plugging in Eq. (S13), we get

$$\beta\langle \dot{\xi}_1^2 \rangle = \int \frac{\mathrm{d}\mathbf{q}}{\mathrm{h}^{3\mathrm{N}}} \int \mathrm{d}\boldsymbol{\xi}\ \ \mathrm{e}^{-\beta\mathrm{V}(\boldsymbol{\xi},\mathbf{q})} \sqrt{\frac{(2\pi)^n|\mathbf{A}|}{\beta}}\,\mathbf{Z}_{11} \tag{S41}$$

Since $\mathbf{A} = \mathbf{Z}^{-1}$ and $|\mathbf{Z}^{-1}| = |\mathbf{Z}|^{-1}$

$$\beta\langle \dot{\xi}_1^2 \rangle = \int \frac{\mathrm{d}\mathbf{q}}{\mathrm{h}^{3\mathrm{N}}} \int \mathrm{d}\boldsymbol{\xi}\ \ \mathrm{e}^{-\beta\mathrm{V}(\boldsymbol{\xi},\mathbf{q})} \sqrt{\frac{(2\pi)^n}{\beta|\mathbf{Z}_\xi|}}\,\mathbf{Z}_{11} \tag{S42}$$

Now, we look at the derivation of $\langle \mathbf{Z}_{11} \rangle$

$$\begin{aligned} \langle \mathbf{Z}_{11} \rangle &= \int \frac{\mathrm{d}\mathbf{q}}{\mathrm{h}^{3\mathrm{N}}} \int \mathrm{d}\boldsymbol{\xi}\ \mathbf{Z}_{11}\mathrm{e}^{-\beta(\frac{1}{2}\mathbf{p}_\mathrm{q}^\mathrm{T}\mathbf{Z}_\mathrm{q}\mathbf{p}_\mathrm{q} + \mathrm{V}(\boldsymbol{\xi},\mathbf{q}))} \int \mathrm{d}\mathbf{p}_\xi\, \mathrm{e}^{-\beta\frac{1}{2}\mathbf{p}_\xi^\mathrm{T}\mathbf{Z}_\xi\mathbf{p}_\xi} \\ &= \int \frac{\mathrm{d}\mathbf{q}}{\mathrm{h}^{3\mathrm{N}}} \int \mathrm{d}\boldsymbol{\xi}\ \mathbf{Z}_{11}\left(\sqrt{\frac{(2\pi)^n}{\beta|\mathbf{Z}_\xi|}}\right)\mathrm{e}^{-\beta\mathrm{V}(\boldsymbol{\xi},\mathbf{q})} \end{aligned} \tag{S43}$$

Hence,

$$\langle \mathbf{Z}_{11} \rangle = \beta\langle \dot{\xi}_1^2 \rangle$$