Technical Report: Optimal estimation of thermodynamic length from equilibrium and nonequilibrium measurements

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We consider the problem of estimating the thermodynamic length of a path in some space of thermodynamic or control parameters from a number of equilibrium simulations or experimental measurements. An asymptotically efficient, differentiable estimate of the metric tensor used in measuring the thermodynamic length and thermodynamic divergence based on the multistate Bennett acceptance ratio estimator is presented. Application to the special cases of passive single-molecule pulling experiments using single and double optical traps is presented.

Recently, there has been a resurgence interest in the concept of *thermodynamic length* [1, 2] due to the observation that pathways of minimal thermodynamic length are "good" pathways for estimating free energies of thermodynamic transformations with minimal statistical error [3].

I. PRELIMINARIES

Consider a system at equilibrium, where the probability of observing an instantaneous configuration $\boldsymbol{x}$ is given by

$$\pi(\boldsymbol{x};\boldsymbol{\lambda}) = Z^{-1}(\boldsymbol{\lambda})\, q(\boldsymbol{x};\boldsymbol{\lambda}) \tag{1}$$

where $q(\boldsymbol{x};\boldsymbol{\lambda}) > 0$ on $\boldsymbol{x} \in \boldsymbol{\Gamma}$ is an unnormalized probability density function, and $Z(\boldsymbol{\lambda})$ is a normalization constant often termed the *partition function*, given by

$$Z(\boldsymbol{\lambda}) = \int_{\boldsymbol{\Gamma}} d\boldsymbol{x}\, q(\boldsymbol{x};\boldsymbol{\lambda}) \tag{2}$$

For systems obeying Boltzmann statistics, the unnormalized density $q(\boldsymbol{x};\boldsymbol{\lambda})$ is given by

$$q(\boldsymbol{x};\boldsymbol{\lambda}) = \exp[-u(\boldsymbol{x};\boldsymbol{\lambda})] \tag{3}$$

where $u(\boldsymbol{x};\boldsymbol{\lambda})$ is termed the *reduced potential*, and $\boldsymbol{\lambda}$ is a vector of one or more thermodynamic or control parameters that define the *thermodynamic state* of the system. For example, following the notation of [4], we could define $\boldsymbol{\lambda}$ for a physical system in a common thermodynamic ensemble (e.g. NVT, NPT, μVT, etc.), as some (sub)set of thermodynamic parameters $\boldsymbol{\lambda} \equiv \{\beta, \boldsymbol{\alpha}, p, \boldsymbol{\mu}\}$ such that

$$u(\boldsymbol{x};\boldsymbol{\lambda}) = \beta[H(\boldsymbol{x};\boldsymbol{\alpha}) + pV(\boldsymbol{x}) + \boldsymbol{\mu}^{\mathrm{T}}\boldsymbol{n}(\boldsymbol{x})] \tag{4}$$

Here, $\boldsymbol{x}$ denotes the instantaneous configuration of the system, with system volume $V(\boldsymbol{x})$ (in the case of a constant pressure ensemble) and $\boldsymbol{n}(\boldsymbol{x})$ the number of molecules of each component of a multi-component system (in the case of a (semi)grand ensemble). For each state t, β_i denotes the inverse temperature, $H_i(\boldsymbol{x})$ the Hamiltonian (which may include an external biasing potential), p_i the external pressure, and $\boldsymbol{\mu}_i$ the vector of chemical potentials of the system components counted by $\boldsymbol{n}(\boldsymbol{x})$. Other thermodynamic parameters and their conjugate variables can be included in a similar manner.

II. THERMODYNAMIC LENGTH

The Fisher information matrix for a fixed value of $\boldsymbol{\lambda}$ is given by

$$I_{ij}(\boldsymbol{\lambda}) = \int_{\boldsymbol{\Gamma}} d\boldsymbol{x}\, \pi(\boldsymbol{x};\boldsymbol{\lambda}) \frac{\partial \ln \pi(\boldsymbol{x};\boldsymbol{\lambda})}{\partial \lambda_i} \frac{\partial \ln \pi(\boldsymbol{x};\boldsymbol{\lambda})}{\partial \lambda_j} \tag{5}$$

$$= \left\langle \frac{\partial u}{\partial \lambda_i} \frac{\partial u}{\partial \lambda_j} \right\rangle_{\boldsymbol{\lambda}} - \left\langle \frac{\partial u}{\partial \lambda_i} \right\rangle_{\boldsymbol{\lambda}} \left\langle \frac{\partial u}{\partial \lambda_j} \right\rangle_{\boldsymbol{\lambda}} \tag{6}$$

$$= \mathrm{cov}\left(\frac{\partial u}{\partial \lambda_i}, \frac{\partial u}{\partial \lambda_j} \right). \tag{7}$$

Then, given the thermodynamic metric tensor $g_{ij}(\boldsymbol{\lambda})$, which is identical to the Fisher information matrix [1],

$$g_{ij}(\boldsymbol{\lambda}) \equiv I_{ij}(\boldsymbol{\lambda}) \tag{8}$$

the thermodynamic length corresponds to the integral along a parameterized path $\boldsymbol{\lambda}(t)$, $t \in [0, \tau]$

$$\mathcal{L} \equiv \int_0^\tau dt\, \left(\dot{\boldsymbol{\lambda}}^{\mathrm{T}}\, \boldsymbol{g}\, \dot{\boldsymbol{\lambda}} \right)^{1/2} \tag{9}$$

where the notation $\dot{\boldsymbol{\lambda}}$ denotes differentiation of the parametric path $\boldsymbol{\lambda}(t)$ with respect to t. The length between $\boldsymbol{\lambda}(0)$ and $\boldsymbol{\lambda}(\mathbf{1})$ will be independent of the parmeterization of the path $\boldsymbol{\lambda}(t)$ — $\mathcal{L}$ depends only on the endpoints.

A related quantity is the *thermodynamic divergence*

$$\mathcal{J} = \tau \int_0^\tau dt\, \dot{\boldsymbol{\lambda}}^{\mathrm{T}}\, \boldsymbol{g}\, \dot{\boldsymbol{\lambda}} \tag{10}$$

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In the special case that $\boldsymbol{\lambda}$ is entirely specified in terms of thermodynamic parameters with associated conjugate variables, as in $u(\boldsymbol{x};\boldsymbol{\lambda}) = u_0(\boldsymbol{x}) + \boldsymbol{\lambda}^{\mathrm{T}}\boldsymbol{v}(\boldsymbol{x})$, then the Fisher information matrix is also identical to the matrix of second partial derivatives $\partial^2\psi/\partial\lambda_i\partial\lambda_j$ of the *free entropy* or *Massieu potential* $\psi(\boldsymbol{\lambda}) \equiv \ln Z(\boldsymbol{\lambda})$ (Eq. 4 in [1]), but the general relationship is actually given by

$$I_{ij}(\boldsymbol{\lambda}) = \frac{\partial^2\psi(\boldsymbol{\lambda})}{\partial\lambda_i\partial\lambda_j} + \left\langle \frac{\partial^2 u(\boldsymbol{x};\boldsymbol{\lambda})}{\partial\lambda_i\partial\lambda_j} \right\rangle_{\boldsymbol{\lambda}} \tag{11}$$

This can be easily verified by differentiation of $\psi(\boldsymbol{\lambda})$ and comparison with Eq. 7 above.

III. ASYMPTOTICALLY OPTIMAL ESTIMATOR FOR THE METRIC TENSOR FROM EQUILIBRIUM DATA

Estimating either the thermodynamic length $\mathcal{L}$ or the thermodynamic divergence $\mathcal{J}$ of a path from equilibrium data collected from some collection of states $\{\boldsymbol{\lambda}_1, \boldsymbol{\lambda}_2, \ldots, \boldsymbol{\lambda}_K\}$ requires an estimator of $g_{ij}(\boldsymbol{\lambda})$. Ideally, this estimator would be continuous, smooth, and differentiable in $\boldsymbol{\lambda}$. Fortunately, we can construct just such an estimator that is also asymptotically optimal using extended bridge sampling, which is identical to the multistate generalization of the Bennett acceptance ratio (MBAR) estimator well-known in statistical mechanics [5].

For a system obeying Boltzmann statistics, the MBAR estimator for the dimensionless free energy $f(\boldsymbol{\lambda}) = -\ln Z(\boldsymbol{\lambda})$ — which estimates $f(\boldsymbol{\lambda})$ only up to an irrelevant constant that is independent of $\boldsymbol{\lambda}$ — is given by

$$\hat{f}(\boldsymbol{\lambda}) = -\ln \sum_{n=1}^{N} \frac{\exp[-u(\boldsymbol{x}_n;\boldsymbol{\lambda})]}{\sum_{k=1}^{K} N_k \exp[\hat{f}(\lambda_k) - u(\boldsymbol{x}_n;\boldsymbol{\lambda}_k]} \tag{12}$$

Here, the sum indexed by n runs over *all* N samples from all states, indexed in arbitrary order, and the sum indexed by k runs over all K states from which N_k equilibrium samples were collected. This expression defines a set of implicit nonlinear equations for the estimators $\hat{f}(\boldsymbol{\lambda}_k)$, $k = 1, \ldots, K$, whose solutions can be determined efficiently in any number of ways [5].

The multistate extended bridge sampling estimator for the Fisher information is

$$\begin{aligned}\hat{g}_{ij}(\boldsymbol{\lambda}) = & \\ & \sum_{n=1}^{N} w_n(\boldsymbol{\lambda}) \left(\frac{\partial u(\boldsymbol{x}_n;\boldsymbol{\lambda})}{\partial\lambda_i}\right)\left(\frac{\partial u(\boldsymbol{x}_n;\boldsymbol{\lambda})}{\partial\lambda_j}\right) \\ & - \left[\sum_{n=1}^{N} w_n(\boldsymbol{\lambda}) \left(\frac{\partial u(\boldsymbol{x}_n;\boldsymbol{\lambda})}{\partial\lambda_i}\right)\right]\left[\sum_{n=1}^{N} w_n(\boldsymbol{\lambda}) \left(\frac{\partial u(\boldsymbol{x}_n;\boldsymbol{\lambda})}{\partial\lambda_j}\right)\right]\end{aligned} \tag{13}$$

where the normalized weight $w_n(\boldsymbol{\lambda})$ is given by

$$w_n(\boldsymbol{\lambda}) \equiv \frac{\exp[\hat{f}(\boldsymbol{\lambda}) - u(\boldsymbol{x}_n;\boldsymbol{\lambda})]}{\sum_{k=1}^{K} N_k \exp[\hat{f}(\boldsymbol{\lambda}_k) - u(\boldsymbol{x}_n;\boldsymbol{\lambda}_k]} \tag{14}$$

[JDC: Huafeng notes that we can abbreviate these complicated expressions using the compact notation from his paper such as $\partial_i u\, \partial_j u$.]

Alternatively, we can write the estimator more compactly in terms of gradient operators with respect to $\boldsymbol{\lambda}$:

$$\begin{aligned}\hat{\boldsymbol{g}}(\boldsymbol{\lambda}) = & + \sum_{n=1}^{N} w_n(\boldsymbol{\lambda})(\boldsymbol{\nabla}_{\boldsymbol{\lambda}} u)(\boldsymbol{\nabla}_{\boldsymbol{\lambda}} u)^{\mathrm{T}} \\ & - \left[\sum_{n=1}^{N} w_n(\boldsymbol{\lambda})\boldsymbol{\nabla}_{\boldsymbol{\lambda}} u\right]\left[\sum_{n=1}^{N} w_n(\boldsymbol{\lambda})\boldsymbol{\nabla}_{\boldsymbol{\lambda}} u\right]^{\mathrm{T}}\end{aligned} \tag{15}$$

where the evaluation of the functions at the corresponding samples $\boldsymbol{x}_n$ at fixed $\boldsymbol{\lambda}$ is implied.

Defining

$$\alpha_i(\boldsymbol{x};\boldsymbol{\lambda}) \equiv \frac{\partial u(\boldsymbol{x};\lambda)}{\partial\lambda_i} \tag{16}$$

we can compactly write

$$\begin{aligned}\hat{g}_{ij}(\boldsymbol{\lambda}) = & \\ & + \sum_{n=1}^{N} w_n(\boldsymbol{\lambda})\, \alpha_i(\boldsymbol{x}_n;\boldsymbol{\lambda})\, \alpha_j(\boldsymbol{x}_n;\boldsymbol{\lambda}) \\ & - \left[\sum_{n=1}^{N} w_n(\boldsymbol{\lambda})\, \alpha_i(\boldsymbol{x}_n;\boldsymbol{\lambda})\right]\left[\sum_{n=1}^{N} w_n(\boldsymbol{\lambda})\, \alpha_j(\boldsymbol{x}_n;\boldsymbol{\lambda})\right]\end{aligned} \tag{17}$$

[JDC: Work out simple form for statistical error in terms of α_i.]

[JDC: Note that I write the variance estimators in this way to make it simpler to derive the asymptotic covariance estimates. Computing estimates of the covariance in this way is not recommended for reasons of numerical precision, since it is possible the result could be negative definite. Instead, we should use:

$$\hat{g}_{ij}(\boldsymbol{\lambda}) = \sum_{n=1}^{N} w_n(\boldsymbol{\lambda})\, [\alpha_i(\boldsymbol{x}_n;\boldsymbol{\lambda}) - \hat{\mu}_i(\boldsymbol{\lambda})]\, [\alpha_j(\boldsymbol{x}_n;\boldsymbol{\lambda}) - \hat{\mu}_j(\boldsymbol{\lambda})]$$

where

$$\hat{\mu_i}(\boldsymbol{\lambda}) \equiv \sum_{n=1}^{N} w_n(\boldsymbol{\lambda})\, \alpha_i(\boldsymbol{x}_n;\boldsymbol{\lambda}) \tag{18}$$

Provided $\alpha_(\boldsymbol{x}_n;\lambda)$ can be rapidly computed for all $\boldsymbol{x}_n$, $n = 1, \ldots, N$ at any $\boldsymbol{\lambda}$, this estimate for the metric tensor $\boldsymbol{g}(\boldsymbol{\lambda})$ can be rapidly computed at any $\boldsymbol{\lambda}$, requiring no further iteration to solve implicit coupled nonlinear equations once the $\hat{f}(\boldsymbol{\lambda}_k)$ have been determined for $k = 1, \ldots, K$. The estimate is continuous, smooth, and differentiable. Calculation of either the thermodynamic

length or thermodynamic divergence along a given path can then proceed through use of any standard quadrature method.

Provided the quadrature error is controlled to be much smaller than the statistical error, the asymptotic covariance estimate for these estimated quantities can provide an assessment of the statistical error in the computed thermodynamic length.

IV. SINGLE OPTICAL TRAP

Consider the case of a single optical trap, in which two polystyrene beads are attached to a polymer (such as a nucleic acid). One bead is fixed to a micropipette, which is fixed at the origin, while the other bead is held in a harmonic optical trap. We consider the simplification to one dimension, where the potential for the bead-and-polymer construct in terms of bead-to-bead distance x is given by some potential $U_0(x)$. The position of the optical trap is given as the control parameter x_0.

Neglecting finite correlation times in generating uncorrelated samples, what is the optimal set of control parameter distances x_0 from which data should be collected?

The reduced potential for this system is written

$$u(x;\boldsymbol{\lambda}) = \beta U_0(x) + \frac{\beta K}{2}(x - x_0)^2 \tag{19}$$

where $\boldsymbol{\lambda} \equiv \{\beta, K, x_0\}$ is the set of thermodynamic and control parameters characterizing the thermodynamic state of this system.

The metric tensor elements for changing only the trap position x_0 can be simply computed from the derivative of the reduced potential

$$\frac{\partial u}{\partial x_0} = -\beta K(x - x_0) \tag{20}$$

which, using Eq. 7, yields

$$g_{x_0,x_0}(\boldsymbol{\lambda}) = \mathrm{var}\left(\delta x/\sigma\right) \tag{21}$$

where $\delta x \equiv x - x_0$, and $\sigma = (\beta K)^{-1}$ is a natural length-scale.

We can also consider the metric tensor elements for other parameters. For example:

$$\frac{\partial u}{\partial x_0} = -\delta x/\sigma \tag{22}$$

$$\frac{\partial u}{\partial K} = \frac{\beta}{2}(\delta x)^2 \tag{23}$$

$$\frac{\partial u}{\partial \beta} = U(\boldsymbol{x};\boldsymbol{\lambda}) \tag{24}$$

and so the diagonal metric tensor elements are

$$g_{x_0,x_0}(\boldsymbol{\lambda}) = \mathrm{var}\left(\delta x/\sigma\right) \tag{25}$$

$$g_{K,K}(\boldsymbol{\lambda}) = \frac{\beta^2}{4}\mathrm{var}\left((\delta x)^2\right) \tag{26}$$

$$g_{\beta,\beta}(\boldsymbol{\lambda}) = \mathrm{var}\left(U\right) \tag{27}$$

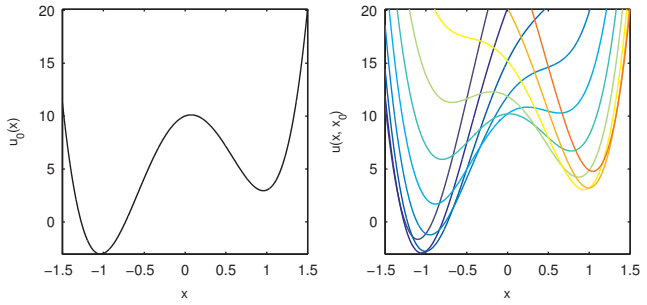

FIG. 1. **Model potential for single optical trap.** Left: Bare potential $u_0(x)$. Right: Total reduced potential $u(x;x_0)$ for ten different values of x_0 spanning the range from -1.5 (blue) to +1.5 (red).

and the off-diagonal elements are

$$g_{x_0,K}(\boldsymbol{\lambda}) = -\frac{\beta}{2}\mathrm{cov}\left(\delta x/\sigma, (\delta x)^2\right) \tag{28}$$

$$g_{x_0,\beta}(\boldsymbol{\lambda}) = -\mathrm{cov}\left(\delta x/\sigma, U\right) \tag{29}$$

$$g_{K,\beta}(\boldsymbol{\lambda}) = -\frac{\beta}{2}\mathrm{cov}\left((\delta x)^2, U\right) \tag{30}$$

A. Numerical results for controlling trap position

We consider a model system similar to [6], where here $u_0(x) \equiv \beta U_0(x) = 10(x^2-1)^2 + 3x$, the trap spring constant $\beta K = 15$ and equilibrium samples are collected for 5 different trap positions x_0. The bare reduced potential $u_0(x)$ is pictured in Fig. 3, along with the total reduced potential $u(x;x_0)$ for several values of x_0.

The dimensionless free energy of the system $f(x_0)$ as a function of trap position x_0 is computed from

$$f(x_0) \equiv -\ln \int_{-\infty}^{+\infty} dx\, e^{-u_0(x;x_0)} + c \tag{31}$$

where c is an arbitrary constant offset (Fig. 2, *left*). The diagonal element of the metric tensor $g_{x_0,x_0}(\boldsymbol{\lambda})$ was computed numerically with K and β held constant for $x_0 \in [-1.5, +1.5]$ according to Eq. 25 (Fig. 2, *middle*). The thermodynamic length, determined by integrating the metric tensor from $x_0 = -1.5$ along a path according to Eq. 9, was also computed numerically (Fig. 2, *right*).

Recently, it was demonstrated that the thermodynamic length $\mathcal{L}(\boldsymbol{\lambda}_a, \boldsymbol{\lambda}_b)$ can provide a bound on the variance of the estimate of the free energy difference $\Delta f_{ab} \equiv f(\boldsymbol{\lambda}_b) - f(\boldsymbol{\lambda}_a)$ estimated from equilibrium samples collected from $\pi(x;\boldsymbol{\lambda}_a)$ and $\pi(x;\boldsymbol{\lambda}_b)$ [3]

$$\mathrm{var}\left(\Delta\hat{f}_{ab}\right) \geq N^{-1}\mathcal{L}^2(\lambda_a, \lambda_b) \tag{32}$$

Equivalently, the per-sample information about Δf_{ab} is related to the inverse of the thermodynamic length:

$$I(\Delta\hat{f}_{ab}) \propto N^{-1}/\mathrm{var}\left(\Delta\hat{f}_{ab}\right) \geq \mathcal{L}^{-2}(\lambda_a, \lambda_b) \tag{33}$$

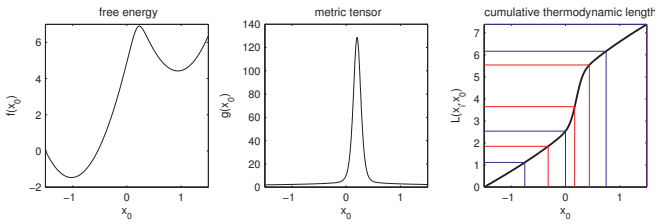

FIG. 2. **Free energy, metric tensor, and thermodynamic length of model potential of single optical trap.** Left: Free energy $f(x_0)$ as a function of trap position x_0. Middle: Thermodynamic metric tensor g_{x_0,x_0} as a function of x_0. Right: Thermodynamic length integrated from $x_0 = -1.5$. Ten equally-spaced points along the thermodynamic length from $x_0 = -1.5$ to $+1.5$ (green) are shown, along with the corresponding values of x_0 (red).

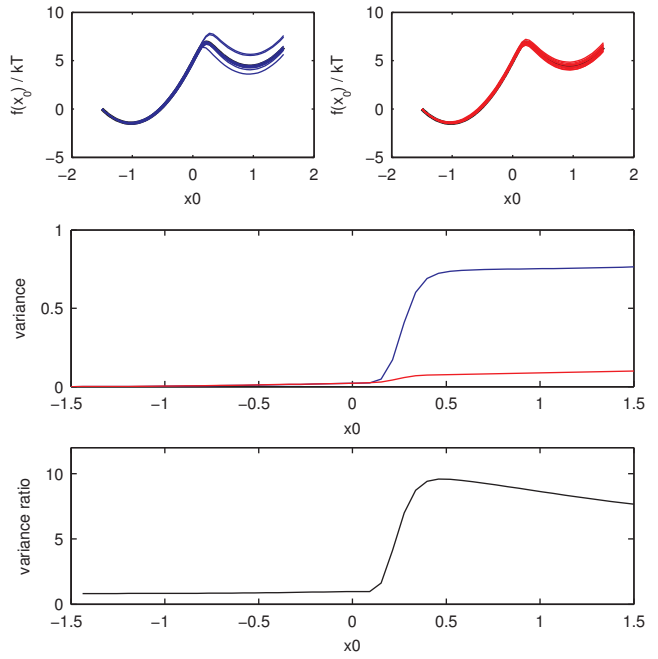

FIG. 3. **Variance in estimates of free energy as a function of trap position for naïve and optimal protocols.** Upper left: MBAR estimate from 10 independent experiments using equally-spaced trap positions from -1.5 to +1.5 (blue) superimposed on true free energy as a function of trap position (black). Upper right: MBAR estimate from 10 independent experiments using trap positions from -1.5 to +1.5 (blue) equidistant in thermodynamic length, superimposed on true free energy as a function of trap position (black). Bottom: Variance in estimate from naïve protocol (blue) and equidistant-length protocol (red) determined from 50 independent experiments.

By choosing to collect data at values of the control parameter x_0 equally spaced in thermodynamic length $\mathcal{L}$, we can (approximately) minimize the variance in estimates of the free energy $f(x_0)$, or equivalently, maximize the per-sample information gain. If we suppose we collect N samples from each of a fixed number M distributions characterized by choices of the trap separation x_0, we can inquire what the average per-sample information gain about $f(x_0)$ is for different choices of the λ parameter.

[JDC: More here.]

V. DOUBLE OPTICAL TRAP

Now we will consider a model with two optical traps, where the micropipette previously holding one of the beads at the origin is now replaced with another harmonic trapping potential. Again this can be simplified to one dimension, with the bead to bead distance in the double harmonic trap set up can be given by a potential $U_0(x)$. The beads in the optical traps will differ in size and therefore result in slightly different spring constants for the trap. The resulting reduced potential will now depend on both spring constants as well as the trap positions. From the experimental set up, as shown in figure 4, a reference coordinate system can be defined. Traps are referred to as trap A and trap B, with Δx_A and Δx_b representing the distance of the bead centers x_A and x_B from the respective centers of the trapping potential. Each trap has an associated spring constant, which are K_A and K_B respectively. In this way a reduced potential depending on the bead centers x_1 and x_2 and the changing trap position of trap A:

$$u(x_1, x_2, x_A) = \beta[\gamma_B(x_2)^2 + U_0(x_1 - x_2) + \gamma_A(x_1 - x_A)^2] \tag{34}$$

where γ_B and γ_A are the reduced srping constans.
It can be shown that as for the single trap potential the metric tensor element for changing the position of trap A, x_A, is given by the derivative of the reduced potential as given in equation20.

$$\frac{\partial u}{\partial x_A} = -\frac{\Delta x_A}{\sigma_A} \tag{35}$$

with Δx_A representing the distance of the bead from the centre of the trap A and σ is the natural length scale as defined before in terms of the spring constant A of trap A. Therefore g is given by:

$$g \equiv \mathrm{var}\left(\frac{\Delta x_A}{\sigma_A}\right) \tag{36}$$

Figure 4 shows a schematic of the experimental set up. [ASJSM: is $var\frac{\Delta x_B}{\sigma_B}$ the same as $var(\frac{\Delta x_A}{\sigma_B})$ get plot to show this]
- issues with reweighting due to averaging of data, new data set?
- is the coordinate system the one we eventually agreed on, or did we end up defining it differently?
- work out efficiency gain
- pmf, thermodynamic length and tensor for set up

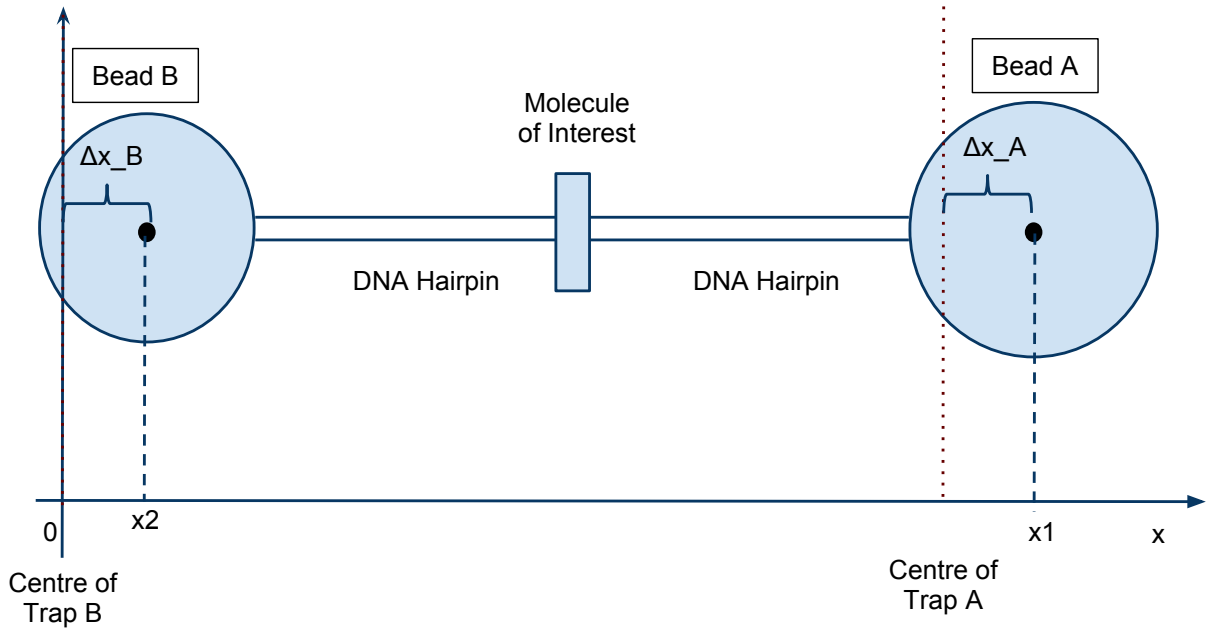

FIG. 4. Temporary schematic that shows the experimental setup. Coordinate system chosen is indicated. Centers of trapping potential are represented by the broken lines. In this set up the trap position of A is varied while, the other position is kept constant.

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