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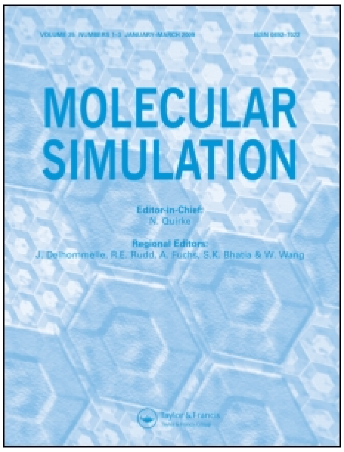

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Gerhard Hummer[a]
[a] Laboratory of Chemical Physics, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA

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FAST-GROWTH THERMODYNAMIC INTEGRATION: RESULTS FOR SODIUM ION HYDRATION

GERHARD HUMMER*

Laboratory of Chemical Physics, Building 5, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892-0520, USA

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Slow-growth thermodynamic integration (TI) is a simple method to calculate free energy differences in fluid and macromolecular systems. A recently derived identity (Jarzynski, C. Phys. Rev. Lett. **78**, 2690, 1997) permits the calculation of free energy differences from repeated TIs at arbitrary growth rates. Here, I investigate the quantitative accuracy of the resulting 'fast-growth' TI for the charging of a sodium ion in water. To estimate the corresponding free energy of hydration, I use simple expressions involving the means and variances of the non-equilibrium work.

Keywords: Nonequilibrium molecular dynamics; Ion solvation; Free energy perturbation theory; Monte Carlo simulation

I. INTRODUCTION

Jarzynski [1, 2] recently derived a remarkable identity between free energy differences and non-equilibrium work averages,

$$\overline{\exp(-\beta W_{0\to1})} = \exp(-\beta\Delta F). \tag{1}$$

Equation (1) relates the Boltzmann-averaged work $W_{0\to1}$ of repeated slow-growth thermodynamic integration (TI) simulations [3 – 11] at arbitrary growth rates to the free energy difference ΔF between two states described by the classical Hamiltonians $\mathcal{H}_0$ and $\mathcal{H}_1$, where $\beta = 1/k_\mathrm{B}T$. The work $W_{0\to1}$

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*Tel.: + 1 (301) 402-6290, Fax: + 1 (301) 495-0825, e-mail: hummer@helix.nih.gov

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is accumulated by changing a coupling parameter λ from 0 to 1 along a prescribed path $\lambda(t)$ in time t,

$$W_{0\to 1}(\tau) = \int_0^\tau dt \frac{d\lambda(t)}{dt} \frac{\partial \mathcal{H}_\lambda}{\partial \lambda}, \tag{2}$$

λ is varied such that the $\lambda(0) = 0$ and $\lambda(\tau) = 1$ states correspond to Hamiltonians $\mathcal{H}_0$ and $\mathcal{H}_1$, respectively, for instance by following a linear path, $\mathcal{H}_\lambda = \mathcal{H}_0 + \lambda(\mathcal{H}_1 - \mathcal{H}_0)$. The average indicated by the bar in Eq. (1) is over an equilibrium ensemble of initial conditions generated according to Hamiltonian $\mathcal{H}_0$ and temperature T, and in the case of stochastic 'time' evolution, additionally over the possible realizations of trajectories for a given initial condition. The identity Eq. (1) is known to hold for 'time' evolution according to Newtonian, Langevin, Nosé-Hoover thermostat, or Monte Carlo (MC) Markov-chain equations of motion, and generally, for Markovian time evolution (in conformation or phase space) governed by a master equation satisfying detailed balance [1, 2, 12]. The identity Eq. (1) is remarkable because it links a non-equilibrium average to an equilibrium thermodynamic potential. In principle, Eq. (1) permits the calculation of free energy differences from repeated 'fast-growth' TIs at arbitrary growth rates. The two limiting cases are the instantaneous change ($\tau \to 0$) which corresponds to standard perturbation from an equilibrium ensemble [13],

$$\langle \exp[-\beta(\mathcal{H}_1 - \mathcal{H}_0)] \rangle_0 = \exp(-\beta \Delta F), \tag{3}$$

and the infinitely slow change ($\tau \to \infty$),

$$\Delta F = \lim_{\tau \to \infty} W_{0\to 1}(t = 0 \to \tau). \tag{4}$$

Here, I investigate the quantitative accuracy of 'fast-growth' TI for the charging of a sodium ion in water.

II. EVALUATION OF THE EXPONENTIAL WORK AVERAGE

Accurate numerical estimates of the exponential work average $\overline{\exp(-\beta W_{0\to 1})}$ from a finite number of 'fast-growth TIs' are difficult [14]. For any finite number of repetitions, that average tends to be dominated by the few smallest values $W_{0\to 1}$ observed. This is a consequence of the strong non-linearity of the exponential function to be averaged. In particular, the estimator $\Delta F_{\mathrm{est}} \equiv -\beta^{-1} \ln[M^{-1} \sum_{i=1}^{M} \exp(-\beta W_i)]$ is biased [15]. The bias disappears in the limit of either infinitely many repetitions (perfect sampling) or infinitely slow growth ($\tau \rightarrow \infty$). To address the problem of accurately estimating $\overline{\exp(-\beta W_{0\rightarrow 1})}$ from a finite number of simulations, I extend numerical integration techniques of conventional TI [16] involving higher-order free energy derivatives evaluated from equilibrium simulations to the non-equilibrium calculation based on Jarzynski's theorem Eq. (1) [1]. This extension is based on an identity derived by Crooks [12] that establishes a connection between the work distributions of the up and down paths ($\lambda(t)$ varied from $\lambda = 0$ to 1, and from 1 to 0, respectively). The free energy can be expressed in terms of cumulants of the $W_{i\rightarrow j}$ distributions [13, 17–23]. The resulting one-sided second-order approximations to the free energy are [24]:

$$\Delta F \approx \overline{W_{0\rightarrow 1}} - \beta\sigma^2_{0\rightarrow 1}/2, \tag{5a}$$

$$\Delta F \approx -\overline{W_{1\rightarrow 0}} + \beta\sigma^2_{1\rightarrow 0}/2, \tag{5b}$$

where $\overline{W_{i\rightarrow j}}$ and $\sigma^2_{i\rightarrow j} = \overline{(W_{i\rightarrow j} - \overline{W_{i\rightarrow j}})^2}$ are the mean and variance of $W_{i\rightarrow j}$, respectively. These correction formulas were derived before by Jarzynski [1], and earlier by Hermans for a special case of diffusional dynamics [25].

In practical applications, it is advantageous to combine information from the up and down paths. This leads to the following symmetric second and fourth-order approximations [24]

$$\Delta F \approx \frac{1}{2}\left(\overline{W_{0\rightarrow 1}} - \overline{W_{1\rightarrow 0}}\right), \tag{6a}$$

$$\Delta F \approx \frac{1}{2}\left(\overline{W_{0\rightarrow 1}} - \overline{W_{1\rightarrow 0}}\right) - \frac{\beta}{12}\left(\sigma^2_{0\rightarrow 1} - \sigma^2_{1\rightarrow 0}\right). \tag{6b}$$

The symmetric average of the up and down work in Eq. (6a) is already widely used in an effort to minimize the so-called hysteresis in slow-growth TI [26]. The weights in the expressions Eq. (6) date back to Hermite [16, 24, 27]. Note that Eq. (6b) is not simply the average of Eqs. (5a) and (5b). Note further that for the expressions Eq. (6) to apply, the systems used in the up and down averages have to be identical. Changes in the solvent particle number, for instance, would affect the work distributions.

III. RESULTS FOR THE CHARGING OF A SODIUM ION IN WATER

In the following, I will illustrate 'fast-growth' TIs for the charging of a sodium ion in water. This test case has been chosen based on the following considerations: (1) The free energy difference between the states 0 (uncharged) and 1 (charged) is large (about 160 $k_{\mathrm{B}}T$), such that estimating the exponential work average is expected to be difficult. (2) Sodium ion hydration has been studied extensively. In particular, system-size effects have been carefully analyzed [17, 28 – 34]. Relatively small system sizes can thus be accounted for, permitting more extensive sampling. (3) Previous studies of this and related systems showed that fluctuations in electrostatic potentials at solute sites are often approximately Gaussian corresponding to linear response [17, 22, 23, 31 – 48]. Based on this observation, the low-order cumulant approximations Eq. (5) and Eq. (6) should be particularly useful.

In the MC simulations, 64 SPC water molecules [49] are used. The sodium ion is modeled as a Lennard-Jones particle with a point charge [5]. Ewald summation is used for the electrostatic interactions. All free-energy results are corrected for self-interactions due to the use of Ewald summation [17]. Additional thermodynamic corrections [31] for the finite dielectric constant of the solvent [34, 47] and for the finite volume occupied by the ion [30, 31] are not included. Further details of the simulations can be found in Refs. [17, 30]. State 0 is an uncharged Lennard-Jones particle in water. In state 1, the sodium ion carries one elementary charge e. The ionic charge is used as the coupling parameter, which is varied linearly in the course of the simulation. After each MC pass (one attempted MC move per particle), the charge is increased (or decreased in the $1 \rightarrow 0$ runs) by an increment e/N, where N is the total number of passes.

Random starting configurations of the charged and neutral solute particle have been equilibrated for 100 000 passes. During another 50 000 passes, configurations have been saved every 100th MC pass, forming ensembles of initial conditions containing 500 configurations each. Starting from these configurations, trajectories are generated using Metropolis MC in which the charge is changed from the initial to the final value ($0 \rightarrow e$ and $e \rightarrow 0$) in a given number N of steps. The energies associated with these charge changes are accumulated to give the work $W_{i \rightarrow j}$ for every TI run. The length of the MC simulations (corresponding to the inverse growth rate) is varied from $N = 200$, 2000, 5000, 10 000, to $N = 100\,000$ MC passes. For $N = 100\,000$, only 50 repetitions each are performed for the up and down TIs.

The results for the mean $\overline{W_{i \rightarrow j}}$ and variances $\sigma^2_{i \rightarrow j}$ are listed in Table I. Table II compiles the results for ΔF calculated from Eqs. (5) and (6). The one-sided formulas Eqs. (5a) and (5b) give results for the free energy of charging the sodium ion between -390 and -406 kJ/mol. The second-order symmetric formula Eq. (6a) has a smaller spread, with results for ΔF between -401 and -404 kJ/mol. The fourth-order symmetric formula

TABLE I Mean and variance of the work for charging and uncharging a sodium ion in water. N is the number of MC passes of the TIs. Results for $200 \leq N \leq 10\,000$ were obtained from 500 repetitions. Results for $N = 100\,000$ were obtained from 50 repetitions. The means and variances are in units of kJ/mol and (kJ/mol)^2, respectively. Statistical errors of one standard deviation are also listed. Errors are estimated by block averaging. The repetitions are divided into K groups. Each group is analyzed separately, and the estimated error for a particular grouping is the square root of K^{-1} times the variance of the results for the K groups. These error estimates are then plotted as a function of $\ln K$. In the limit of small K, the groups become statistically independent, and the error estimates fluctuate around a plateau. This plateau value is reported as the error

N	$\overline{W_{0\to1}}$	$\sigma^2_{0\to1}$	$\overline{W_{1\to0}}$	$\sigma^2_{1\to0}$
200	-272.7 ± 3.3	653.8 ± 42.0	529.0 ± 2.8	687.8 ± 60.0
2000	-358.8 ± 1.5	233.2 ± 20.0	445.8 ± 2.0	198.8 ± 16.0
5000	-380.4 ± 0.8	105.8 ± 7.0	426.5 ± 1.5	109.3 ± 7.0
10000	-390.2 ± 0.6	70.0 ± 5.0	417.6 ± 1.2	71.7 ± 5.0
100000	-402.4 ± 0.4	6.1 ± 2.0	405.5 ± 0.6	8.3 ± 1.2

Eq. (6b) shows the smallest variance (excluding the shortest $N = 200$ runs) with results for ΔF between -403.3 and -403.9 kJ/mol. Also included are results for the direct exponential averages, Eq. (1). The large and systematic errors of the straightforward application of Eq. (1) are caused in part by the strong bias of the estimator [15].

For reference, I also calculated the free energy of charging by using conventional TI. The first and second derivative of the free energy with respect to the ion charge [17, 50] were calculated at $q = 0$, $0.5e$, and e from MC simulations at fixed ion charge covering 50 000 passes for equilibration and 630 000 passes for production. The total of 2 040 000 passes is roughly equivalent to the 2 100 000 passes of the 500 up and down 'fast-growth' TIs over $N = 2000$ passes, with 50 000 passes each at $q = 0$ and $q = e$ for the generation of initial conditions. The equilibrium derivative data are combined using the multi-derivative integration formulas of Ref. [16]. The sixth-order formula using two derivatives each at the endpoints, and one at $q = 0.5e$, gives a free energy difference of -404.7 ± 0.7 kJ/mol. This is in full agreement with the 'fast-growth' results of Table II. However, the statistical error of conventional TI is estimated to be only about one third of the $N = 2000$ 'fast-growth' result using the fourth-order symmetric expression Eq. (6b). Figure 1 compares the results for ΔF as a function of the total number of MC passes. The estimated statistical errors from 50 simulations of 100 000 MC passes are smaller than those of 500 simulations of 10 000 MC passes (Tab. II). This is expected from a more detailed analysis [24] which shows that the 'optimum' allocation of computer time is achieved if the standard deviation of the work is on the order of $k_{\mathrm{B}}T$. From the 50 simulations of 100 000 MC, we estimate a standard deviation of the work of

TABLE II Free energies for charging the sodium ion using different expressions involving means and variances of the work distribution, as well as direct exponential averages. N is the number of MC passes in the slow-growth TIs. The free energies are in units of kJ/mol. The statistical errors of the estimates in columns one to four are based on linear error propagation, assuming errors of means and variances as listed in Table I. The statistical errors of the exponential estimates (columns six and seven) are estimated from block averaging by dividing the data into ten blocks

N	$\overline{W_{0\to1}}$ $-\beta\sigma^2_{0\to1}/2$	$-\overline{W_{1\to0}}$ $+\beta\sigma^2_{1\to0}/2$	$(\overline{W_{0\to1}}$ $-\overline{W_{1\to0}})/2$	$(\overline{W_{0\to1}} - \overline{W_{1\to0}})/2-$ $\beta(\sigma^2_{0\to1} - \sigma^2_{1\to0})/12$	$-\beta^{-1} ln\ \overline{exp(-\beta W_{0\to1})}$	$\beta^{-1} ln\ \overline{exp(-\beta W_{1\to0})}$
200	-404.6 ± 9.1	-390.2 ± 12.4	-400.9 ± 2.2	-399.7 ± 3.9	-342.9 ± 5.0	-470.2 ± 5.0
2000	-405.9 ± 4.3	-405.7 ± 3.8	-402.3 ± 1.3	-403.5 ± 2.0	-391.0 ± 2.5	-408.0 ± 4.5
5000	-401.8 ± 1.6	-404.4 ± 2.1	-403.4 ± 0.8	-403.3 ± 1.2	-397.2 ± 1.3	-408.5 ± 1.8
10000	-404.3 ± 1.2	-403.1 ± 1.6	-403.9 ± 0.7	-403.8 ± 1.0	-401.5 ± 0.5	-399.7 ± 2.0
100000	-403.6 ± 0.6	-403.8 ± 0.6	-403.9 ± 0.4	-403.9 ± 0.5	-403.5 ± 0.5	-403.9 ± 0.6

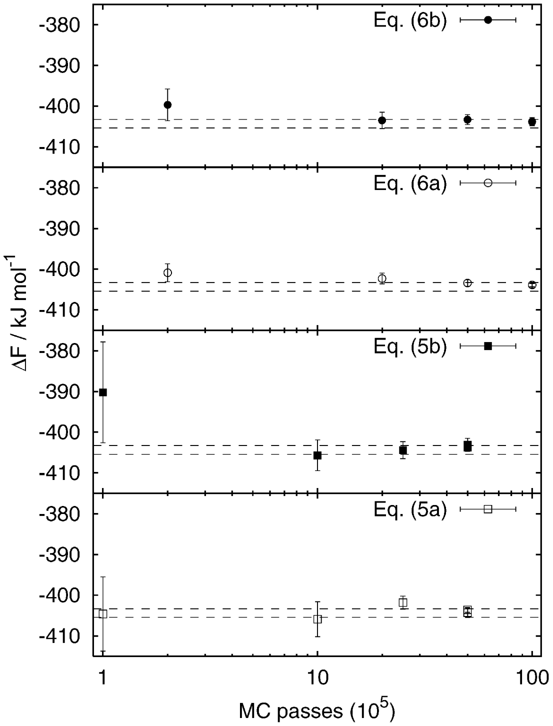

FIGURE 1 Free energies of charging a sodium ion in water calculated from the one-sided (bottom two panels) and two-sided formulas (top two panels) as a function of the total number of MC passes (all runs combined for a given inverse growth rate *N*). Dashed lines indicate the reference value from TI (one standard deviation).

about 1.1 k_BT, whereas the 500 runs of 10 000 MC passes have a larger standard deviation of about 3.4 k_BT (Tab. I). Moreover, for slow runs we expect smaller systematic errors of the approximate free energy expressions Eqs. (5) and (6) [24].

IV. CONCLUDING REMARKS

Free energy differences can be calculated from slow-growth TI at arbitrary growth rates based on a theorem by Jarzynski [1, 2]. Here, simple expressions [24] are used to combine 'fast-growth' results optimally into a free energy estimate. These expressions involve means and variances of the work determined from TI with arbitrary growth rates. Means and variances can be calculated accurately from relatively few repetitions, making these formulas practically relevant. For the charging free energy of a sodium ion in water ($\Delta F \approx 160 k_B T$), the 'fast-growth' TI results are consistent with conventional thermodynamic integration. The present work demonstrates that highly accurate free energy differences can be calculated from 'fast-growth' TI. But clearly, further testing is required, in particular for conformational or binding free energies.

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