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Macromolecular Entropy Can Be Accurately Computed from Force

Ulf Hensen,[†] Frauke Gräter,[‡] and Richard H. Henchman*[,§,∥]

[†]ETH Zürich, Biosystems Science and Engineering, Mattenstrasse 26, 4058 Basel, Switzerland

[‡]Heidelberg Institute for Theoretical Studies, Schloss-Wolfsbrunnenweg 35, 69118 Heidelberg, Germany

[§]Manchester Institute of Biotechnology, The University of Manchester, 131 Princess Street, Manchester M1 7DN, United Kingdom

[∥]School of Chemistry, The University of Manchester, Oxford Road, Manchester M13 9PL, United Kingdom

Supporting Information

ABSTRACT: A method is presented to evaluate a molecule's entropy from the atomic forces calculated in a molecular dynamics simulation. Specifically, diagonalization of the mass-weighted force covariance matrix produces eigenvalues which in the harmonic approximation can be related to vibrational frequencies. The harmonic oscillator entropies of each vibrational mode may be summed to give the total entropy. The results for a series of hydrocarbons, dialanine and a β hairpin are found to agree much better with values derived from thermodynamic integration than results calculated using quasiharmonic analysis. Forces are found to follow a harmonic distribution more closely than coordinate displacements and better capture the underlying potential energy surface. The method's accuracy, simplicity, and computational similarity to quasiharmonic analysis, requiring as input force trajectories instead of coordinate trajectories, makes it readily applicable to a wide range of problems.

INTRODUCTION

The computation of entropy from atomistic simulations is both of great interest and a long-standing challenge. A system's entropy may be written as

$$S = -k_B \int p(\mathbf{p}, \mathbf{q}) \log p(\mathbf{p}, \mathbf{q}) \mathrm{d}\mathbf{p}\mathrm{d}\mathbf{q} \quad (1)$$

in terms of the probability distribution function $p(\mathbf{p},\mathbf{q})$ over momenta $\mathbf{p}$ and coordinates $\mathbf{q}$. While the momentum term can be integrated analytically as separable Gaussian distributions for each atom, the high-dimensionality and extensive correlations in configuration space make intractable the exact computation of S. This problem is avoided in the evaluation of the *difference* in entropy. Methods such as thermodynamic integration (TI),[1] exponential averaging,[2] the Jarzynski equality,[3] or umbrella sampling[4] directly yield free energy differences, which in turn lead to entropy differences either as the negative of the temperature-derivative of the free energy difference or by subtracting the free energy difference from the enthalpy difference and dividing by temperature.[5] Notably, these methods avoid the explicit evaluation of $p(\mathbf{q})$ and instead determine how $p(\mathbf{q})$ changes along a reaction coordinate from one state to the other. They usually make use of multiple intermediate states, which is computationally demanding and limits the size of the structural or chemical difference between the two states.

Unlike an entropy difference relative to another state, directly evaluating the entropy of a system of interest circumvents the need for having end-points to define a difference, yields the entropy from a single simulation rather than many, and allows a comparison of states of arbitrary separation. However, the evaluation of entropy makes inevitable a more complex and detailed formulation based on integrating over the total configuration space. Here we consider how to determine the intramolecular entropy of a single molecule. A long-standing method is normal mode (NM) analysis, which uses the energy's second-derivative, namely its curvature.[6] It approximates the energy by a multivariate harmonic potential, diagonalizes the Hessian at the energy minimum, and evaluates the vibrational frequencies and harmonic-oscillator entropies from each normal mode's eigenvalues. It neglects the contribution of multiple energy minima and configurations away from these minima, typically resulting in an underestimation of the configurational entropy, for which frequency scaling[7] and calculations over multiple minima are possible remedies.

The second method, termed quasiharmonic (QH) analysis, derives a multidimensional harmonic potential from the coordinate fluctuations about the average structure measured in an equilibrium simulation.[8−10] Eigenvalues from the diagonalized covariance matrix of the mass-weighted coordinates lead to vibrational frequencies and entropies. Anharmonicity can lead to an overestimation of entropies[10,11] if the coordinate distributions extend over multiple minima or because of nonlinear correlations between modes. Various approaches exist to correct for anharmonicity and nonlinear pairwise correlations,[12−16] including whether to use Cartesian or internal coordinates.[9−11,17,18] Other methods go beyond the harmonic approximation and use coordinate distributions $p(\mathbf{q})$ in eq 1 with no assumptions about the shape of the potential. They may integrate each coordinate separately[19−23] or use nonparametric density estimators in internal[24] or Cartesian

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coordinates.[25,26] Alternative strategies use transition probabilities from step-by-step reconstructions[27,28] or the spectral density derived from the velocity autocorrelation function.[29,30] Despite these developments, NM and QH analysis with their conceptual simplicity are still by far the most commonly used methods to determine intramolecular entropy.

Proposed here is a method to calculate a molecule's intramolecular entropy that has the conceptual simplicity of NM and QH analysis but overcomes the limitations of nonharmonic coordinate distributions. Instead of energies, curvatures or coordinates, we use first derivative of the energy, namely, atomic forces, from an equilibrium ensemble of structures generated in a simulation. Such a strategy has been successfully applied to calculate the entropy of liquids,[31−35] solutions,[36−39] and bound complexes.[40,41] It resembles thermodynamic integration[1] and force-based umbrella sampling,[42,43] which calculate the potential of mean force along a specific reaction coordinate, but instead involves forces along all the coordinates. Conceptual advantages of using forces over coordinates are that force distributions are highly harmonic,[33] forces more directly capture atomic correlations than coordinates, and they reduce spurious diffusive motions. Also, the average force, being zero at equilibrium, is better defined than an average structure, which is often unrealistic and highly contorted for a flexible system. We evaluate and compare entropies using forces, QH analysis and TI for a selection of linear hydrocarbons, dialanine, and a β hairpin, test systems from earlier work.[26] We find the new force-based method to be significantly more accurate than QH analysis, making it an attractive method for calculating intramolecular entropies of macromolecules.

THEORY

We rederive the QH entropy equation based on coordinate covariance and present alongside a new, almost identical derivation for the entropy in terms of force covariance (FC). This is related to an equation derived earlier[33] for the entropy of liquid water in terms of squared forces, which only considered implicitly the diagonal terms of the full FC matrix. For a particle undergoing harmonic motion in one dimension, the average potential energy $\langle U\rangle$ is

$$\langle U\rangle = \frac{1}{2}k\langle \Delta q^2\rangle = \frac{1}{2}\langle F^2\rangle/k \tag{2}$$

where k is the force constant, $\Delta q = q - \langle q\rangle$ is the particle's position q minus the average position $\langle q\rangle$, F is the force on the particle, and the second equality uses the relationship $F = -k\Delta q$. Converting to mass-weighted coordinates $q' = m^{1/2}q$ and mass-weighted forces $F' = m^{-1/2}F$ and substituting $\omega^2 = k/m$ for a harmonic oscillator, where ω is the angular frequency and m is the particle's mass, these equations become

$$\langle U\rangle = \frac{1}{2}\omega^2\langle \Delta q'^2\rangle = \frac{1}{2}\langle F'^2\rangle/\omega^2 \tag{3}$$

Given that $\langle U\rangle = (1/2)k_BT$ for a harmonic oscillator, where k_B is Boltzmann's constant and T is temperature, this leads to two possible equations for ω:

$$\omega^q = \sqrt{\frac{k_BT}{\langle \Delta q'^2\rangle}} \tag{4}$$

and

$$\omega^F = \sqrt{\frac{\langle F'^2\rangle}{k_BT}} \tag{5}$$

where ω^q and ω^F are the angular frequencies from the first and second equalities in eq 3, respectively.

These equations may be generalized to N atoms each with three Cartesian coordinates. The mass-weighted coordinate covariance matrix σ^q has elements defined in terms of mass-weighted coordinates q' as

$$\sigma^q_{ij} = \langle \Delta q_i' \Delta q_j'\rangle \tag{6}$$

while the mass-weighted force covariance matrix σ^F has elements defined in terms of mass-weighted forces F' as

$$\sigma^F_{ij} = \langle F_i' F_j'\rangle \tag{7}$$

Diagonalization of σ^q yields $3N$ eigenvalues λ_i^q, which relate to ω_i^q by

$$\omega_i^q = \sqrt{\frac{k_BT}{\lambda_i^q}} \tag{8}$$

Similarly, diagonalization of σ^F leads to $3N$ eigenvalues λ_i^F, which relate to ω_i^F by

$$\omega_i^F = \sqrt{\frac{\lambda_i^F}{k_BT}} \tag{9}$$

The total entropy may be calculated from coordinate-derived or force-derived angular frequencies using either the expression for a classical harmonic oscillator

$$S_{cl} = k_B\sum_{i=1}^{3N}\left(\log\frac{k_BT}{\hbar\omega_i} + 1\right) \tag{10}$$

or a quantum harmonic oscillator

$$S_{qm} = k_B\sum_{i=1}^{3N}\left(\frac{\hbar\omega_i/k_BT}{e^{\hbar\omega_i/k_BT} - 1} - \log(1 - e^{-\hbar\omega_i/k_BT})\right) \tag{11}$$

FC provides an averaged vibrational entropy over all energy basins but no explicit information on how many energy basins are present. Instead, it returns a harmonic potential that is a weighted average of all basin widths. This effect is demonstrated for an example sextic potential $U(x) = x(x + 1)(x + 1.8)^2(x - 1.3)^2 + 1.3689$ in Figure 1 for the case of $\langle U\rangle = 1/2$ and $m = 1$. Under these conditions, $k_BT = 0.618$ and the configurational partition function is 0.662. The effective harmonic force constant calculated using $q = (2\pi k_BT/k)^{1/2}$ is found to be 8.9. For the FC harmonic potential, $k = \langle F^2\rangle = 8.0$, which is in good agreement with the numerically determined value. This is in contrast to NM analysis, for which the harmonic potential is derived from the second derivative at the global minimum, giving $k = 13.2$, which is too high, and to QH analysis for which $k = 1/\langle \Delta q^2\rangle = 3.3$, which is too low. This demonstrates that FC, by using thermalized configurations, automatically produces lower frequencies than NM analysis, whose frequencies at the local minimum are often scaled to match experiment,[7] but higher frequencies than QH analysis whose coordinate fluctuations span all energy basins. On the other hand, similar to NM analysis, a more complete estimate of the FC entropy requires the logarithm of the number of energy basins. For the alkane systems, three minima per dihedral are assumed, such that an additional term $S = (N-3)k_B$

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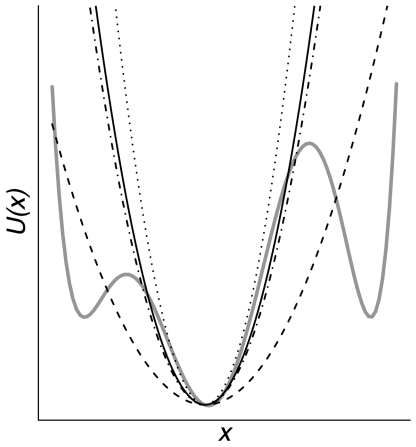

Figure 1. Schematic illustrating different ways of fitting a harmonic potential to a model potential $U(x) = x(x + 1)(x + 1.8)^2(x - 1.3)^2 + 1.3689$ (solid thick gray), namely, by numerical integration (solid black), normal mode (NM) analysis (dotted), quasiharmonic (QH) analysis (dashed), and force covariance (FC) (dot-dashed) at $\langle U \rangle = 1/2$ and $m = 1$.

log 3 is included in the total entropy. This term is ignored for dialanine and the β hairpin, which are dominated by a small number of minima.

METHODS

The test systems were set up as described elsewhere.[26] Briefly, force-field parameters were obtained from the Dundee Prodrug server[44] based on the GROMOS united-atom force field.[45] Stochastic dynamics simulations were performed using the molecular simulations package GROMACS[46] in vacuo at 400 K with friction constant $\gamma = 10$, dielectric constant $\varepsilon = 1$, integration step size of 0.0005 ps, and no bond constraints. Positional restraints with $k = 25000$ kJ mol^{-1} nm^{-2} were applied to three terminal atoms and contribute to the total force in eq 7. These restraints ensure consistency with the TI calculations[25] with which we compare. The systems were isotropically coupled to a pressure bath at 1 bar ($\tau = 1.0$ ps).[47] Unless otherwise stated, data-collection simulations were run for 12.5 ns and forces and coordinates were saved at 50 frames per ps, equating to 5 000 000 data points. Another point to note is that the forces F_i inputed into eq 7 are half the force measured in the simulation to avoid double-counting pairwise forces.[31,32]

Exact entropies for these systems have been calculated elsewhere using TI with respect to a reference state.[25] Briefly, the entropy was calculated using $S = (E - A)/T$, where E was the total energy measured directly from the simulation, and the Helmholtz energy was calculated using $A = A_0 - \Delta A$. ΔA in turn was the Helmholtz energy to perturb the molecule to a state consisting of N noninteracting particles in harmonic wells, which has an analytically solvable Helmholtz energy A_0. Three atoms of each molecule were harmonically restrained to ensure a better convergence of the TI calculation. Because the translational and rotational motions are suppressed by these restraints, the $3N$ vibrational modes are present rather than $3N - 6$ for the intramolecular entropy of a freely translating and rotating molecule. Given the high value of the restraints, it may be noted that the entropy obtained is almost entirely intramolecular.

A modified GROMACS tool is available online at http://personalpages.manchester.ac.uk/staff/henchman/software/.

RESULTS AND DISCUSSION

We test FC on a range of gas-phase molecules: (i) the seven n-alkanes from butane to decane, (ii) dialanine, and (iii) a 14-residue β hairpin of protein G (GB1), all held by restraints as explained earlier. Figure 2 shows the classical (eq 10) and

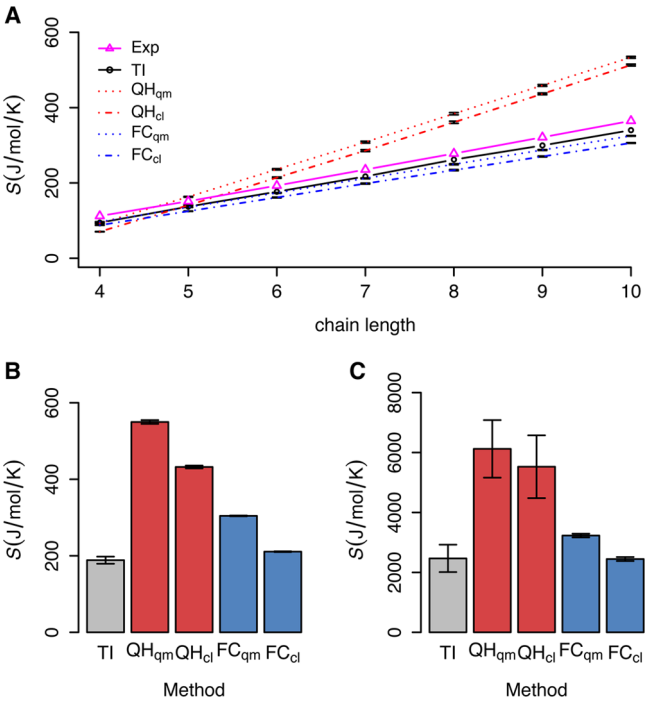

Figure 2. Intramolecular entropies derived by various methods. Entropies of (A) n-alkanes from butane to decane, (B) dialanine, and (C) the GB1 β-hairpin. Exp: restrained experimental values derived from ref 48 (see Supporting Information, Table S1). TI: thermodynamic integration to a reference state.[26] QH_{qm}: quantum quasiharmonic. QH_{cl}: classical quasiharmonic. FC_{qm}: quantum force covariance. FC_{cl}: classical force covariance. Error bars indicate confidence intervals as 1.96 standard deviations, obtained from five different simulations each ($N = 5$).

quantum oscillator (eq 11) entropies with vibrational frequencies evaluated either from coordinates (eq 8) or from forces (eq 9) versus the TI values[25] and equivalent restrained experimental values all at 400 K. The calculation of the restrained experimental entropies from the experimental gas-phase values[48] is described in the Supporting Information. The error bars indicate confidence intervals of the mean and are equal to 1.96 standard deviations calculated from five separate simulations. When comparing with TI, the classical entropies are the relevant quantities. While the agreement between all methods is close for the smallest molecule butane, the QH entropies exceed the TI reference entropy for the larger molecules, being more than double for dialanine and the β hairpin. These findings are consistent with earlier findings.[11] In contrast, FC achieves consistently better agreement with TI for all the alkanes, dialanine, and the β hairpin. Additionally, the FC entropies have significantly lower errors than QH entropies by up to an order of magnitude for the larger molecules. When comparing with experiment, the quantum values are the relevant quantities. TI entropies lie slightly below experimental

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values by a similar amount to the difference between classical and quantum harmonic oscillator entropies, suggesting that the TI values differ because of the neglect of quantum effects. However, incomplete sampling, the approximate force-field, and the approximate accounting for of the restraint may also contribute.

Why the FC entropies are lower than the QH entropies is evident from a comparison of their wavenumbers $\nu = 2\pi\omega/c$, with c the speed of light (Figure 3). With the exception of the highest-frequency modes, the FC wavenumbers are larger than the QH wavenumbers, and decrease more slowly and evenly than the QH wavenumbers, which rapidly drop after a few eigenvectors. Moreover, the lowest-frequency QH wavenumbers are lower than the FC wavenumbers. This may be more easily seen by visualizing the eigenvectors in terms of their coordinate amplitudes. The coordinate amplitudes for QH eigenvectors $\mathbf{u}_i^q$ are given by $x_{ij} = (\lambda_i^q/m_j)^{1/2}u_{ij}^q$, and for the FC eigenvectors $\mathbf{u}_i^F$ by $x_{ij} = (k_BT/(\lambda_i^F m_j)^{1/2})u_{ij}^F$, where u_{ij}^q and u_{ij}^F are the respective eigenvector elements of eigenvector i and atom j. Figure 3B exemplifies the magnitudes of the x component of the coordinate-based eigenvectors $\mathbf{u}_i^q$ and its force-based analogs $\mathbf{u}_i^F$ for decane (for all three signed components, see Supporting Information, Figure S2). QH amplitudes are about an order of magnitude larger than FC amplitudes, and only a few QH eigenvectors describe much of the coordinate fluctuations, whereas more FC eigenvectors contribute more substantially. The same trend holds for the other hydrocarbons, dialanine, and the β hairpin. The larger differences between classical and quantum values for dialanine and the β hairpin arise from their higher frequencies, a consequence of their stronger intramolecular interactions than in the alkanes.

The extent of harmonicity and rate of convergence of the two methods may be further assessed by carrying out principal component analysis. Figure 4 plots for decane the trajectories of the first two QH principal components $\sigma^q\mathbf{u}_i^q$ and the first two FC principal components $\sigma^F\mathbf{u}_i^F$. The FC principal components become harmonic much more rapidly, mostly after 2 ns, whereas the QH principal components remain anharmonic even after 100 ns. This helps explain the larger errors and slower convergence of QH entropies in the case of the hydrocarbons as seen in Supporting Information Figure S1. However, the same figure shows that the QH and FC entropies of dialanine and the β hairpin converge at much more similar rates, namely after 20 ns. This is despite FC values agreeing much better with TI than QH as examined earlier. Figure S1 shows that both coordinate and force entropies are fairly insensitive to the number of sample points as long as points are saved at least once per 1 ps. Interestingly, unlike QH entropies which increase in time, FC entropies are seen to decrease with longer simulation lengths or more sampling points.

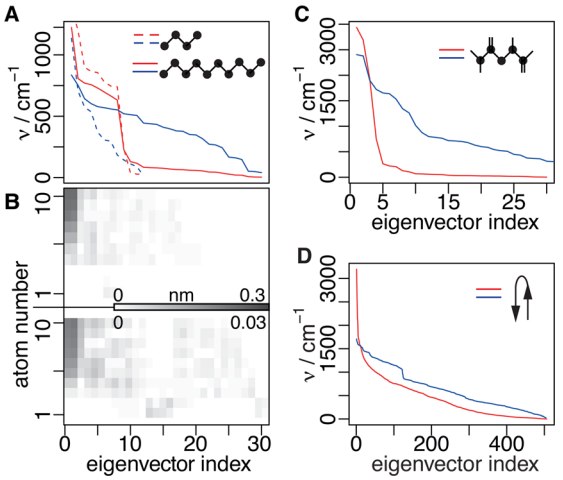

Figure 3. Eigenvalue-derived wavenumbers and eigenvectors. (A) Wavenumber spectra for the QH (red) and FC (blue) methods for butane (dashed) and decane (solid). (B) eigenvector displacements in the x-direction for the QH (upper) and FC (lower) methods. Note the different scales for QH and FC. Wavenumber spectra for (C) dialanine and (D) the β hairpin, colored as in part A.

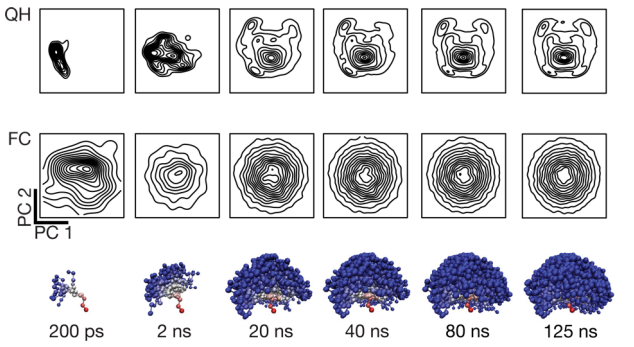

Figure 4. Principal component analysis of the eigenvectors. QH (top) and FC (middle) principal component (PC) 2 versus the respective PC 1 for decane as a function of sampling time. The bottom row displays the matching sampled configurations of decane.

CONCLUSIONS

A method has been presented to evaluate a molecule's intramolecular entropy from the atomic forces measured in a molecular dynamics simulation. Diagonalization of the mass-weighted force covariance matrix produces eigenvalues which may be converted into harmonic frequencies and thus entropies. The resulting FC entropies are found to agree much better with the in-principle exact but computationally expensive values from TI than those from QH analysis, which substantially overestimates entropies. This may be attributed to a number of factors. First, the force distributions along the respective eigenvectors are shown to be much more harmonic than the coordinate distributions. Second, the FC method separates the vibrational harmonic entropy from the entropy over different conformers. Admittedly, the model used here to evaluate the conformational entropy is still rather crude but the errors in this approach are evidently much less than errors in the QH approximation. The difficulty in sampling and explicitly accounting for all conformational states[49] remains unsolved but is outside the scope of this paper. Third, the average force, being zero, is a more robust quantity than the average structure which may be quite contorted for flexible molecules. Using forces also minimizes superposition problems for which there is no universal approach, but the effect of tumbling has not been fully explored in this study, given that the restraints used to aid the TI calculations impose a fairly fixed frame of reference. An added advantage of FC is that it should readily be extended to systems of multiple molecules by being completely compatible with theories already developed for liquids[31−35] and solutions.[36−39] Given that FC yields more accurate entropies with equivalent computational expense to the widely used QH method and similar to NM analysis, it is expected to significantly expand the usefulness of entropy calculations in

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understanding the behavior of molecular systems. This in turn should make entropy a more accessible and useful quantity.

■ ASSOCIATED CONTENT

Supporting Information

Supporting methods. Table S1: Experimental hydrocarbon gas-phase entropies and components to calculate the restrained entropies. Figure S1: Effect of sampling frequency and simulation length. Figure S2: Eigenvectors of butane and decane. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: henchman@manchester.ac.uk.

Notes

The authors declare no competing financial interest.

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