Boltzmann’s $H$-Function and Diffusion Processes

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Supporting Information

ABSTRACT: There exists a generalization of Boltzmann’s $H$-function that allows for nonuniformly populated stationary states, which may exist far from thermodynamic equilibrium. Here we describe a method for obtaining a generalized or collective diffusion coefficient $D$ directly from this $H$-function, the only constraints being that the relaxation process is Markov (short memory), continuous in the reaction coordinate, and local in the sense of a flux/force relationship. As an application of this $H$-function method, we simulate the self-consistent extraction of $D$ via Langevin/Fokker–Planck (L/FP) dynamics on various potential energy landscapes. We observe that the initial epoch of relaxation, which is far removed from the stationary state, provides the most reliable estimates of $D$. The construction of an $H$-function that guarantees conformity with the second law of thermodynamics has been generalized to allow for diffusion coefficients that may depend on both the reaction coordinate and time, and the extension to an arbitrary number of reaction coordinates is straightforward. For this multidimensional case, the diffusion tensor must be positive definite in the sense that its eigenvalues must be real and positive. To illustrate the behavior of the proposed collective diffusion coefficient, we simulate the $H$-function for a variety of Langevin systems. In particular, the impacts on $H$ and $D$ of landscape shape, sample size, selection of an initial distribution, finite dynamic observation range, stochastic correlations, and short/long-term memory effects are examined.

INTRODUCTION

Diffusion processes play a key role in understanding and controlling the transport of matter, energy, momentum, and even information in physics, chemistry, material science, biology, and communications technology. Descriptions of diffusion range from abstract mathematical formulations to predicting the behavior of neutrons in nuclear reactors to understanding the spread of infectious diseases throughout a population. Given the generality and importance of this process, enormous resources have been committed to measurement, modeling, and theoretical formulations. At present, there are three commonly used methods for extracting diffusion coefficients from experimental data.

For instance, one might hypothesize the existence of some diffusion mechanism such as Fickian dispersion or stochastic hopping, solve the appropriate equations or simulate the diffusion process, and extract a diffusion coefficient or its tensor analogue. One would then compare the predictions of this model to carefully selected experimental data, and evaluate the significance of discrepancies in order to decide whether modifications or improvements to the original model are warranted. This iterative process is repeated until there is a satisfactory match between theory and measurement.

On the other hand, at the microscopic level, one might possess detailed information concerning the trajectories of individual molecules or entities and then attempt to identify the self or tracer diffusion process that most faithfully characterizes these observations. In both the collective and self-diffusion scenarios, the diffusion coefficient or tensor extracted from this measurement/theory comparison depends on the details of the iterated model.

In the spirit of fluctuation theory, suppose that one is supplied with a continuous, time-dependent stochastic variable $x(t)$ along with the random Fourier component of the Dirac delta function $\delta(x(t))$, which is $\exp(igx(t))$, where $g$ is a Fourier wave vector. Further assume that one can measure or construct the time correlation function of the Fourier component in some stationary state ensemble that is ergodic, so that time and ensemble averages may be interchanged. If these two nontrivial conditions are satisfied, then a generalized diffusion coefficient $D$ can be extracted from the $g^2$ dependence of the exponential decay in $t$ of this correlation function, referred to as a dynamic structure factor (DSF). However, there may exist situations in which instrumental and physical limitations preclude an accurate determination of the DSF, and so the question arises: “Is there a method that determines $D$ which does not require the construction of a time correlation function from fluctuations?” Moreover, is there a relatively model-free method applicable to situations in which the system may be far from thermodynamic equilibrium or even far from a stationary state?

Here we present a formulation of diffusion that relies only on the second law of thermodynamics along with relatively few additional assumptions regarding the nature of the underlying physical processes. In the first part of this paper, the development of the generalized $H$-function formulation is...
presented for single and multiple dimensions. In the second part of this paper, we demonstrate that the estimated diffusion coefficient obtained with this formulation is both accurate and robust, and we illustrate its use via Langevin simulations. We expect that these investigations will facilitate the application of the generalized H-function formulation to estimate D from experimental systems.

**Generalized H-Function.** To identify a method for determining D that does not require the construction of a time correlation function from fluctuations and is relatively model free, consider the following generalization of Boltzmann’s H-function for the continuous random variable x.

\[
H(t) = \int dx P(x, t) \ln \left[ \frac{P(x, t)}{P_0(x)} \right]
\]  

(1)

which allows for a nonuniform stationary state density \(P_0(x)\), which may exist far from thermodynamic equilibrium. This functional form has been associated with a variety of names, including the Gibbs entropy postulate, the relative entropy, the entropy production, the stochastic free energy, and the Kullback–Leibler divergence. It has been used to characterize the dissipation of free energy and the direction and length of the “arrow of time.” It plays a fundamental role in the development of information theory and in algorithms for pattern recognition.

The time derivative of \(H(t)\) is given by

\[
\frac{dH(t)}{dt} = \int dx \frac{\partial P(x, t)}{\partial t} \ln \left[ \frac{P(x, t)}{P_0(x)} \right]
\]  

(2)

of which motivates the introduction of a local probability flux, \(J(x, t)\), through

\[
\frac{\partial P(x, t)}{\partial t} = -\frac{\partial}{\partial x} J(x, t)
\]  

(3)

We now have

\[
\frac{dH(t)}{dt} = -\int dx \frac{\partial J(x, t)}{\partial x} \ln \left[ \frac{P(x, t)}{P_0(x)} \right]
\]  

(4)

which we integrate by parts and require that the system be closed so that \(J(x, t) \equiv 0\) at both upper and lower boundaries. Then,

\[
\frac{dH(t)}{dt} = \int dx J(x, t) \frac{\partial}{\partial x} \ln \left[ \frac{P(x, t)}{P_0(x)} \right]
\]  

(5)

At this point, assume that the dynamics conform to a Markov process, so that the time interval “dt” is significantly longer than the correlation time associated with the intrinsic noise within the system. This implies the existence of either a stationary state or a monotonic decrease in \(H(t)\) with increasing t:

\[
\frac{dH(t)}{dt} \leq 0
\]  

(6)

Insofar as we are concerned with the continuum limit for dynamics on a class of Markov chains, \(P_0(x)\) is unique and can be regarded as the “equilibrium probability density”. Equation 6 is sometimes regarded as a statement of the second law of thermodynamics. Now deduce the simplest form for the probability flux that guarantees the inequality in eq 6 on the condition that the system resides in the state \(x\) at time \(t\), namely, that

\[
J(x, t) = -LP(x, t) \frac{\partial}{\partial x} \ln \left[ \frac{P(x, t)}{P_0(x)} \right]
\]  

(7)

Here L is a positive, constant coefficient associated with the dissipative (heat producing) process (diffusion). This form for \(J(x, t)\) is consistent with LFP dynamics. Finally, identify \(L\) with the diffusion coefficient \(D\), so that

\[
\frac{dH(t)}{dt} = -D \int dx \left( \frac{\partial P(x, t)}{\partial x} \right)^2 P(x, t)
\]  

(8)

In irreversible thermodynamics, a local, dynamic chemical potential, \(\mu(x, t)\), is defined as

\[
\mu(x, t) = \ln \left[ \frac{P(x, t)}{P_0(x)} \right]
\]  

(9)

so that

\[
\frac{dH(t)}{dt} = -D \int dx \left( \frac{\partial \mu(x, t)}{\partial x} \right)^2 P(x, t)
\]  

(10)

In this context, \(D\) can be expressed as the ratio of the rate of decay of \(H\) to the second moment of a dynamic chemical potential gradient. Insofar as this ratio can be obtained directly from relaxation/simulation data, \(D\) is independent of any further assumptions concerning the nature of the underlying physical processes.

This result is a special case of a very general derivation that was first implied by the work of Lebowitz and Bergmann and also extended by Santamato and Lavenda Santamato. These authors allowed for an \(N \times N\) component diffusion tensor, \(\hat{D}\), which could depend on time as well as on the reaction coordinate set \(\{X\}\):

\[
\frac{dH(t)}{dt} = -\sum_{i=1}^{N} \sum_{j=1}^{N} \int d^N x D_{ij} \mu(\{X\}^N, t) P(\{X\}^N, t) \left[ \frac{\partial \mu(\{X\}^N, t)}{\partial x_i} \right] \left[ \frac{\partial \mu(\{X\}^N, t)}{\partial x_j} \right]
\]  

(11)

where \(D_{ij}\) is the element in row i and column j of \(\hat{D}\) and the chemical potential is given by

\[
\mu(\{X\}^N, t) = \ln \left[ \frac{P(\{X\}^N, t)}{P_0(\{X\}^N)} \right]
\]  

(12)

Equation 11 follows directly from assuming Langevin/Fokker-Planck (LFP) dynamics on some \(N\)-dimensional potential energy landscape whose shape is given by \(-\ln P_0(\{X\}^N)\). Here it should be noted that Lebowitz and Bergmann considered a system with deterministic internal dynamics but with boundary interactions that were stochastic and impulsive. In the limit of high collision frequency with the boundaries, the collision operator can be expanded to second order in the derivative with respect to \(\{X\}\), which results in a Fokker-Planck description of the dynamical evolution. After several intermediate steps, this leads to eq 11, which is the multidimensional generalization of eq 10. In order for \(H(t)\) to decrease monotonically with increasing t, the local, dynamic diffusion tensor \(\hat{D}\) must be positive definite in the sense that its eigenvalues must, everywhere and always, be positive.
D must be Hermitian in order for the second law of thermodynamics to hold,25 which implies Onsager symmetry, i.e., $D_{ij} = D_{ji}$. Note that this symmetry is valid without any appeal to fluctuation theory restricted to small deviations from the stationary state. D must be a symmetric tensor even if the system evolves far from the stationary state. Under LFP dynamics, the tensor D is a covariance matrix with diagonal elements describing fluctuation magnitude in each dimension and off-diagonal elements describing covariance/correlation across dimensions. As such, D must be symmetric and positive definite.

If any of the eigenvalues of the diffusion tensor happen to vanish, then the stationary distribution is no longer unique. Multiple stationary states will appear, and the one eventually attained will depend strongly on the initial distribution. This glass-like behavior will manifest itself even if one or more eigenvalues of D vanish only over some fraction of the landscape, provided that the region contains the basin of an attractor.

Associated with eq 11 is a probability flux given by

$$
J_i((X)^N, t) = -\sum_{j=1}^{N} D_{ij}((X)^N, t) P((X)^N, t) \frac{\partial \mu_i((X)^N, t)}{\partial x_j}
$$

(13)

Therefore, the flux along the coordinate $x_i$ depends on the probability that the system is at the set of coordinates $(X)^N$ at time $t$ as well as on the $N$-dimensional chemical potential gradient. The point is that the system is not closed with respect to motion along the $x_i$ coordinate and so L/FP dynamics projected into this subspace need not conform with a monotonic decrease of $H(t)$ as $t$ increases. That is, ignoring degrees of freedom that affect the behavior of the population along the $x_i$ coordinate can lead to an apparent violation of the second law of thermodynamics. This implies that $H(t)$ can serve as a general, although crude, indicator of the landscape’s dimensionality and shape.

At this point, it is tempting to associate the labels $(i, j)$ with distinct chemical species, in which case we are dealing with mass diffusion in an $N$ component system.25 A relation between the Boltzmann and mass diffusion tensors is a topic with both theoretical and practical implications, and a careful study is beyond the scope of this investigation. However, we offer the conjecture that, given the validity of L/FP dynamics, the symmetric component of the appropriate mass diffusion tensor $\tilde{D}_M$ can be identified with the Boltzmann H-tensor $\tilde{D}_i$; i.e.,

$$
\tilde{D} = \frac{1}{2}(\tilde{D}_M + \tilde{D}_M^T)
$$

(14)

where $X^T$ denotes the transpose of $X$. This relation should hold even if the mass diffusion process occurs far from thermodynamic equilibrium. If the above conjecture is valid, the fact that the symmetric part of $\tilde{D}_M$ must be positive definite allows for rigorous tests of internal consistency in diffusion coefficient databases for multicomponent systems.

**ESTIMATING A DIFFUSION COEFFICIENT, $D$, FROM RELAXING DISTRIBUTIONS**

Equation 8 can be rewritten as

$$
D = \frac{\int dx \left( \frac{\partial}{\partial x} \ln \left( \frac{P(x, t)}{\overline{P}(x)} \right) \right)^2 P(x, t)}{\int dx \left( \frac{\partial}{\partial x} \ln \left( \frac{P(x, t)}{\overline{P}(x)} \right) \right)^2}
$$

(15)

providing an estimator for $D$ that only requires knowledge of the stationary-state probability density, $\overline{P}(x)$, the nonstationary state density, $P(x, t)$, and the time derivative of their relative entropy, $(d/dt)H(t)$. For the purpose of discussion, let us refer to the denominator of eq 15 as

$$
I(t) = \int dx \left( \frac{\partial}{\partial x} \ln \left( \frac{P(x, t)}{\overline{P}(x)} \right) \right)^2 P(x, t)
$$

(16)

We begin by examining a simple hypothetical system that can be solved analytically. Specifically, we consider a population that is normally distributed with mean 0 at all times and whose variance is a function of time, $\sigma^2(t)$, with $0 < \sigma^2(t) < \infty$. Note that the relaxation over time of this population is an Ornstein–Uhlenbeck process and is completely described by $\sigma^2(t)$.

The following equalities are easily derived for this example:

$$
D = \frac{1}{2} \int dx \left( \frac{\partial}{\partial x} \ln \left( \frac{P(x, t)}{\overline{P}(x)} \right) \right)^2 = \frac{d}{dt} \frac{\sigma^2(t)}{\sigma^2(\infty)}
$$

(17)

$$
I(t) = \sigma^2(t) \frac{1}{\sigma^2(\infty)} - \frac{1}{\sigma^2(t)}
$$

(18)

$$
H(t) = \frac{1}{2} \left( \frac{\sigma^2(t)}{\sigma^2(\infty)} + \ln \left( \frac{\sigma^2(\infty)}{\sigma^2(t)} \right) - 1 \right)
$$

(19)

$$
\frac{dH}{dt} = \frac{1}{2} \left( \frac{1}{\sigma^2(\infty)} - \frac{1}{\sigma^2(t)} \right) \frac{d}{dt} \sigma^2(t)
$$

(20)

We choose to set $D = 1$ on the arbitrary time scale of days. We also set $\sigma^2(0) = 0.01$ and $\sigma^2(\infty) = 1$, so that the population begins as a narrow normal distribution and relaxes to a standard normal in its stationary state. Equation 17 then yields

$$
\frac{d}{dt} \sigma^2(t) = 2(1 - \sigma^2(t))
$$

which can be used to solve for $\sigma^2(t)$ analytically or numerically, given that $\sigma^2(0) = 0.01$. A plot of $\sigma^2(t)$ is shown in Figure 1.

![Figure 1. Plot of $\sigma^2(t)$ versus day used in analytic example.](image)

**INFLUENCE OF NOISE IN ESTIMATED DENSITIES**

Throughout the remainder of the paper, estimated quantities are denoted with a circumflex symbol; that is, $\hat{X}$ is an estimate of $X$. $\hat{D}$ is the ratio of $-(dH(t)/dt)$ to $\hat{H}(t)$; thus, $\hat{D}$ tends to be most stable when $-(dH(t)/dt)$ and $\hat{H}(t)$ tend to be large. Because $H(t)$ is bounded below by 0 and $H(t)$ is monotonically decreasing, $\hat{H}(t)$ tends to be convex, at least over course-
grained time intervals. That is, \( \hat{H}(t) \) and \(-dH(t)/dt\) tend to be decreasing functions in \( t \). For constant \( D \), eq 8 shows \(-dH(t)/dt\) \( \propto I(t) \). Thus, when \( \hat{H}(t) \) is convex, \( \hat{I}(t) \) tends to also decrease in time. For this reason, estimates of \( D \) are most stable soon after the population is initialized/perturbed.

We illustrate this point in our analytic example by treating \( \sigma^2(t) \) as if it were estimated via maximum likelihood with \( D \) degrees of freedom each time the population is observed. That is, we use \( \hat{\sigma}^2(t) = (\sigma^2(t) \chi^2_{DF}(t_i))/DF \), where \( \chi^2_{DF}(t_i) \) represents an independent random variable from a \( \chi^2 \)-distribution with \( D \) degrees of freedom corresponding to the noise at time \( t_i \). We then compute \( \hat{H}(t) \) and \( \hat{I}(t) \) at each time point using \( \hat{\sigma}^2(t) \) in place of \( \sigma^2(t) \), and \( \hat{\sigma}^2(\infty) \) in place of \( \sigma^2(\infty) \). The resulting noise in \( \hat{H}(t) \) can be greatly reduced, but not fully eliminated, via a smoothing operation. Figure 2 summarizes the distribution of point estimates of \( D \), after smoothing via multispontaneous regression, for 50 simulated relaxations for each of several values for \( DF \). As can be seen, the approach suggested by eq 15 yields correct \( D \) estimates for this hypothetical Ornstein–Uhlenbeck relaxation process. The variability in estimates of \( D \) at the first time point (0.025 days) is large due to the difficulty in estimating the slope at a boundary when the slope is not constant near the boundary. For these simulations, aside from the first time point, the variability in \( \hat{D} \) clearly increases as \( DF \) decreases or as \( \hat{H}(t) \) decreases (and \( t \) increases).

**Estimating \( D \) without Knowledge of the Stationary State.** A diffusive system evolves to its stationary state asymptotically, meaning the population is not truly in its stationary state until after an infinite period of relaxation. In systems with barriers, the population may take a very long time to even remotely resemble the stationary state. For this reason, we now consider the impact of approximating the stationary state with the state observed at time \( T \).

In our analytic Ornstein–Uhlenbeck relaxation example, this corresponds to replacing the variance of the stationary state, \( \sigma^2(\infty) \), with the variance at the last observed time, \( \sigma^2(T) \), when computing \( \hat{H}(t) \) and \( \hat{I}(t) \). Let \( \hat{D}(t, T) \) denote the estimate of \( D \) obtained at time \( t \) when using \( \sigma^2(T) \) in place of \( \sigma^2(\infty) \). When \( t \to T \), \( \hat{D}(t, T) \) provides very poor estimates of \( D \) as can be seen analytically. Indeed

\[
\frac{d}{dt} \left( \frac{\hat{D}(t, T)}{D} \right) = \frac{1}{\sigma^2(T)} \frac{d}{dt} \frac{\hat{\sigma}^2(t)}{\sigma^2(\infty)} \frac{1}{\left( 1 - \frac{\sigma^2(t)}{\sigma^2(T)} \right)^2} \frac{d}{dt} \hat{\sigma}^2(t)
\]

(21)

which has a quadratic singularity as \( t \to T \). This illustrates that when the stationary state is not known but is approximated by a distribution observed at a “late” time, \( T \), in the relaxation process, there can be a severe bias in the estimate of \( D \) when \( t \) is close to \( T \), as displayed in Figure 3. All values of \( T \) provided reasonable estimates of \( D \) for \( t \) close to 0, indicating that it would be beneficial to observe this relaxing system as frequently as possible at early time points. Additionally, the range of time in which \( \hat{D}(t, T) \) well approximates \( D \) increases rapidly with \( T \), which suggests that when the true stationary state cannot be observed one should estimate the stationary state for this system by observing the population as late as possible.

We present some analytic insights as to what general characteristics the approximating state should have in order to provide a good estimate of \( D \). Suppose the population distribution at time \( t \) is given by \( P(x,t) \) and let \( P(x,\infty) = P_{ss}(x) \). We now examine the error in \( dH/dt \) and \( I \) caused by using some other fixed distribution \( g(x) \) in place of \( P_{ss}(x) \). Let us denote which distribution is being used as a reference with a subscript as in the following example: \( H_{ss}(t) = \int dx P(x,t) \ln(P(x,t)/g(x)). \) To simplify the presentation, we omit the \( x \) dependence and write \( P(t), P_{ss} \) and \( g \) for \( P(x, t), P_{ss}(x) \), and \( g(x) \), respectively.

We have

\[
H_{ss}(t) = H_g(t) + \int dx P(t) \ln \left( \frac{g}{P_{ss}} \right)
\]

(22)

and

\[
\frac{d}{dt} H_{ss}(t) = \frac{d}{dt} H_g(t) + \int dx \frac{\partial}{\partial t} \left[ P(t) \ln \left( \frac{g}{P_{ss}} \right) \right]
\]

\[
= \frac{d}{dt} H_g(t) + \int dx \frac{g}{P_{ss}} \frac{\partial}{\partial t} P(t)
\]

(23)

(since \( P_{ss} \) and \( g \) are fixed in \( t \))

This form shows that differences between \( P_{ss} \) and \( g \) in regions of \( x \) where \( P(t) \) is not changing in time, or is changing very slowly, do not strongly affect an estimate of \( dH(t)/dt \). Similarly,
which yields

$$I_{i,j}(t) = I_j(t) + \int dx P(t) \left[ \frac{d}{dx} \ln \left( \frac{g}{P_{i,j}} \right) + \frac{d}{dx} \ln \left( \frac{g}{P_{i,n}} \right) \right]$$

This form shows that regions of $x$ where $P(t) = 0$, $P_{i,n} \propto g$, or $P(t) \propto (P_{i,n})^{1/2}$ do not cause a difference between $I_{i,n}(t)$ and $I_j(t)$.

**Diffusion with Barriers.** Barriers may prevent a relaxing system from reaching the stationary state within the limited time a system may be monitored. For this reason, we examine the implications of the preceding conclusions for a system with barriers. In particular, we examine whether $g(x)$ must closely resemble $P_{i,n}(x)$, which may take an indefinite amount of time to observe, in order to obtain an accurate estimate of $D$.

One may characterize a system with barriers by partitioning the reaction coordinate into wells such that the subpopulation within each well tends to rapidly explore its own well, but when barriers are large, subpopulations from different wells mix very slowly. Suppose that $\mathcal{W}_X = \{w_1, w_2, ..., w_N\}$ forms such a partition of the reaction coordinate $X$. The distribution at time $t$ of any population may be written as

$$P(x, t) = \sum_{n=1}^{N} \pi_n(t) P_n(x, t)$$

such that
\[
\int_{x \in \nu_n} \text{d}x P_n(x, t) = 1 \text{ for all } n \text{ and } t
\]

\[
P_n(x, t) = 0 \text{ for all } x \text{ not contained in } \nu_n, \text{ for all } n \text{ and } t
\]

\[
\sum_{n=1}^{N} \pi_n(t) = 1 \text{ for all } t
\]

where \( P_n(x, t) \) is the distribution at time \( t \) of the subpopulation within well \( n \) and \( \pi_n(t) \) is the proportion of the total population in well \( n \) at time \( t \). Similarly, the stationary state may be written as

\[
P_n(x) = P(x, \infty) = \sum_{n=1}^{N} \pi_n xss_n(x)
\]

where \( xss_n(x) \) is the stationary state distribution of the subpopulation within well \( n \) and \( \pi_n \) is the proportion of the total population in well \( n \) in the stationary state.

The characteristic of a relaxation path whose progression to \( P_n(x) \) is impeded by the presence of barriers is that the distribution at each well becomes very similar to that of the stationary state long before the distribution of the population across wells appears like the stationary state. That is, after a short time \( T \),

\[
g(x) = P(x, T) \approx \sum_{n=1}^{N} \pi_n(T) xss_n(x)
\]

where \( \pi_n(T) \neq \pi_n \).

If \( \frac{\text{d}}{\text{d}t}\pi_n(t) = 0 \) for all \( n \) and \( t \), then \( \pi_n(t) = \pi_n \) for all \( n \) and so trivially \( g(x) \approx P_n(x) \), meaning the stationary state can be well approximated at time \( T \). We consider a more interesting scenario of when the relaxation of the system becomes glass-like due to barriers, so that \( \frac{\text{d}}{\text{d}t}\pi_n(t) \approx 0 \) for all \( n \) (with \( \frac{\text{d}}{\text{d}t}\pi_n(t) > 0 \) for at least two \( n \)). In this case,

\[
\int \text{d}x \ln \left( \frac{g}{P_n} \right) \frac{\partial}{\partial t} P(t) = \sum_{n=1}^{N} \int_{x \in \nu_n} \text{d}x \ln \left( \frac{h}{P_n} \right) \frac{\partial}{\partial t} P(t)
\]

\[
= \sum_{n=1}^{N} \ln \left( \frac{\pi_n(T)}{\pi_n} \right) \int_{x \in \nu_n} \text{d}x \frac{\partial}{\partial t} P(t)
\]

\[
= \sum_{n=1}^{N} \ln \left( \frac{\pi_n(T)}{\pi_n} \right) \frac{\partial}{\partial t} \pi_n(t) \approx 0
\]

Thus, by eq 23, \( \frac{\text{d}}{\text{d}t}H_p(t) \approx \frac{\text{d}}{\text{d}t}H_p(t) \).

Similarly,

\[
\int \text{d}x P(t) \left[ \frac{\partial}{\partial x} \ln \left( \frac{P(t)}{P_n(x)} \right) \right] = \sum_{n=1}^{N} \int_{x \in \nu_n} \text{d}x P(t) \left[ \frac{\partial}{\partial x} \ln \left( \frac{P(t)}{P_n(x)} \right) \right]
\]

\[
= \sum_{n=1}^{N} \int_{x \in \nu_n} \text{d}x P(t) \left[ \frac{\partial}{\partial x} \ln \left( \frac{P(t)}{P_n(x)} \right) \right]
\]

\[
= \sum_{n=1}^{N} \int_{x \in \nu_n} \text{d}x P(t) \left[ \frac{\partial}{\partial x} \ln \left( \frac{P(t)}{P_n(x)} \right) \right] = 0
\]

Thus, by eq 25, \( I_p(t) \approx I_p(t) \).

The exercise above shows that when mixing between wells is slow, to obtain an accurate estimate of \( D^* \), knowledge of the stationary state is not required. Any state after the distribution within each well has stabilized may be used in place of the stationary state to estimate \( D \). We illustrate this point in Figure 4, which displays estimates of \( H, I, \) and \( D \) obtained when using \( \hat{P}(x, 1) \) (red) and \( \hat{P}_n(x) \) (black) for Langevin simulations in four different landscape scenarios. In the plots of \( H \), the black and red lines are roughly parallel, so their derivatives are roughly equal. For \( I \), the red and black curves are nearly indistinguishable from one another. As shown in the bottom row, estimates of \( D \) obtained using either \( \hat{P}(x, 1) \) or \( \hat{P}_n(x) \) are accurate and very similar to one another, even when \( \hat{P}(x, 1) \) and \( \hat{P}_n(x) \) are very different.

**D as a Function of Time or Reaction Coordinate.** Equation 8 can be generalized in one dimension to allow diffusion to be a function of time, \( t \), or the reaction coordinate, \( x \), as

\[
\frac{dH(t)}{dt} = -\int \text{d}x D(x, t) \left( \frac{\partial}{\partial x} \ln \left( \frac{P(x, t)}{\hat{P}(x)} \right) \right)^2 P(x, t)
\]

(31)

If diffusion is a function of \( t \) but remains constant in \( x \) for a given \( t \), then we have \( dH(t)/dt = -dH(t)/dt(t) \), which suggests one can estimate diffusion as a function of time, \( D(t) \), in the same manner as one can estimate a constant diffusion. We illustrate this result in Figure 5, which shows accurate diffusion function estimates until \( H(t) \) becomes small.

![Figure 5](image-url)

Figure 5. Results for three simulations of 5000 particles diffusing in a parabolic landscape (i.e., \( P(x, 0) = \text{normal}(0, 1) \) and \( \hat{P}_n(x) = \text{normal}(0, 1) \)). \( D(t) = 2 - (t/(0.05 + t)) \) (left) and \( 1 + (t/(0.05 + t)) \) (right).

When diffusion is a function of \( x \), the diffusion function must remain inside the integral in eq 31 and generally cannot be well-estimated with the proposed approach. Using the proposed approach in this case extracts an estimate of \( D^* \), defined as

\[
D^* = \int \text{d}x D(x, t) \left( \frac{\partial}{\partial x} \ln \left( \frac{P(x, t)}{\hat{P}_n(x)} \right) \right)^2 P(x, t)
\]

(32)

In some cases, one can find a transformation of the reaction coordinate \( w(x) \) such that \( D(w(x)) \) is a constant. For example, in systems for which \( D(x) \propto x^2 \), using \( w(x) = \ln(x) \) will yield \( D(w(x)) \) as a constant.
Diffusion with Memory and Stochastic Correlations. Additional explorations into the effectiveness of estimating \( D \) from relaxation profiles are presented in the Supporting Information. In particular, we demonstrate the expected behavior that estimated diffusion increases when a temporal memory is added to the diffusive (velocity) fluctuations and decreases in the presence of strong stochastic correlations across population members.

Choosing an Initial Distribution. There is an obvious asymmetric in the roles of \( P(x, t) \) and \( \hat{P}(x) \) in eq 15. Consideration of this asymmetry provides valuable insight regarding experimental design. In particular, to obtain a reasonable estimate of \( D \) at time \( t \), \( \hat{P}(x, t) \) and \( \hat{P}_\alpha(x) \) must provide reasonable estimates of \( P(x, t) \) and \( \hat{P}_\alpha(x) \), respectively, across the entire set \( \{x : P(x, t) > 0\} \), where \( \{x : \text{condition}\} \) denotes the values of \( x \) for which condition is true. That is, one can only obtain estimates of \( D \) at time points for which \( \{x : P(x, t) > 0\} \) is within the dynamic observation range of the measurement system (note that \( \{x : \hat{P}_\alpha(x) > 0\} \) need not be contained within the dynamic observation range). Additionally, the existence of an \( x \) for which \( \hat{P}(x, t) > 0 \) and \( \hat{P}_\alpha(x) = 0 \) will cause \( \hat{E}(t) = \hat{I}(t) = \infty \), resulting in an undefined estimate of \( D \). However, the existence of an \( x \) for which \( \hat{P}(x, t) = 0 \) and \( \hat{P}_\alpha(x) > 0 \) presents no problem because \( \log(0) = \ln(0^0) = \ln(1) = 0 \). These observations suggest that it is best to use an initial distribution that is as far from the estimated stationary state distribution as possible. One can now employ analytical approximations to the delta function, such as

\[
\delta(x - x_c, 0) = \lim_{\alpha \to \infty} \frac{\alpha}{\pi \alpha^2 (x - x_c)^2 + 1}
\]

\[
\frac{d}{dx} \ln \delta(x - x_c, 0) = \lim_{\alpha \to \infty} \frac{-2\alpha^2 (x - x_c)}{\alpha^2 (x - x_c)^2 + 1} = - \frac{2}{x - x_c}
\]

\[
\lim_{t \to 0} \frac{dH(t)}{dt} = -4D \int \frac{\delta(x - x_c)}{(x - x_c)^2} + \text{nonsingular terms}
\]

The right-hand side of eq 36 is dominated by a quadratic divergence that is independent of the form of \( \hat{P}_\alpha(x) \). The implication here is that, in order to get an accurate estimate for \( D \), one should extract a rather narrow distribution for the initial state and rely on short/medium temporal ranges to deduce the rate of decay of \( H(t) \).

Selecting an initial distribution that is close to the estimated stationary state can produce very poor estimates of \( D \). Consider the behavior of \( \hat{D} \) as \( H(t) \to 0 \) when each time point has a unique set of observations and corresponding estimated density. Note that both \( \hat{H}(t) \) and \( \hat{I}(t) \) are strictly positive, and only if \( \hat{P}(x, t) = \hat{P}_\alpha(x) \). When \( \hat{P}_\alpha(x) \) is estimated by the observations collected at time \( T \) (i.e., \( \hat{P}_\alpha(x) = \hat{P}(x, t) \)), then \( \hat{H}(t), \hat{I}(t), \forall t \neq T \). Even when a system is in its stationary state, \( \hat{E}(t) > 0 \) and \( \hat{I}(t) > 0 \), where \( \hat{E}(t) \) denotes the expected or average value of \( Y \). As \( t \to \infty \), \( \hat{H}(t) \) and \( \hat{I}(t) \) become dominated by \( \hat{E}(t) \) and \( \hat{E}(t^2) \), respectively. A smoothing operation that constrains \( \hat{H}(t) \) to be monotonically decreasing will show \( \frac{d}{dt} \hat{H}(t) \to 0 \). That is, the numerator of \( \hat{D} \) will go to zero as \( t \to \infty \) and the denominator will be strictly positive and randomly fluctuate around \( \hat{E}(t) \). Thus, \( \hat{D} \) will go to zero as \( t \to \infty \). A smoothing operation that does not constrain \( H(t) \) to be monotonic will show \( \frac{d}{dt} \hat{H}(t) \) fluctuating around \( 0 \), producing some negative estimates of \( D \). The point here is that, if the initial distribution is not sufficiently far from the estimated stationary state distributions, the resulting estimates of \( D \) will be poor.

Estimating the Uncertainty in \( \hat{D} \). The uncertainty for \( \hat{D} \) can be estimated using non-parametric bootstrapping by repeating the following general protocol in each of many iterations. Within iteration \( m \), complete the following steps. For each observation time point \( t \), at which \( \hat{N} \) observations were originally recorded, create a bootstrap sample by sampling with replacement \( \hat{N} \) times from the set of original observations. Using the bootstrap samples, estimate a new density for each time point and recalculate \( \hat{D}_m(t) \) using the density estimates of the bootstrap samples. After repeating this process \( M \) times, one gets a collection of estimates \( \{\hat{D}_m(t)\}_{m=1}^M \) for each time point. The standard error for the original estimate of \( D \) at time point \( t \) can be approximated by the standard deviation of \( \{\hat{D}_m(t)\}_{m=1}^M \).

CONCLUSIONS

Our principal conclusion here is that it is feasible to extract, with good accuracy, diffusion coefficients directly from relaxation data, with a minimum number of physical assumptions. While our derivation was based on L/FP dynamics, our simulations strongly indicate that the \( H \)-function method of estimating \( D \) is valid for systems with a temporal memory and for interactions between particles. We have shown that this technique is computationally robust; moreover, in the case of a landscape with one or more barriers, it is not even necessary to have knowledge of the stationary state probability density. In contrast to the dynamic structure factor, which requires the construction of a time correlation function of fluctuations relative to the stationary state, the \( H \)-function method requires knowledge of relaxation dynamics far from the stationary state, and does not depend on the ergodicity of the system. Since, by design, it maximizes the relaxation signal relative to the noise, it is most useful in situations where spurious noise sources or sampling limitations make it difficult to estimate \( D \) via fluctuation methods. For a multidimensional diffusion process, the diffusion tensor \( \hat{D} \) possesses the Onsager symmetry (i.e., \( D_{ij} = D_{ji} \)) as a consequence of the second law of thermodynamics, independent of the proximity to equilibrium or to the stationary state. \( \hat{D} \) therefore has a key property of a covariance matrix.

We anticipate that our formulation, simulations, and statistical approaches will provide a framework for estimating a diffusion coefficient to many experimental systems, not just simulations, where diffusion occurs in a limited number of
dimensions. Unlike solving a specific diffusion equation, the method we describe does not require that we make assumptions about the underlying geometry in which particles are diffusing. From a practical point of view, it would be interesting to explore the conditions under which it is possible to obtain information about the coordinate and time dependence of $D$. From a theoretical viewpoint, it would be interesting to see if it is possible to associate a diffusion coefficient with dynamics on an arbitrary Markov chain (network). As for the thermodynamic significance of Boltzmann’s $H$-function, consider the isothermal case in which the system is in contact with a thermal reservoir. Given the uniqueness of the stationary state, one could ask whether it is possible to associate an $H$-function, $H(t)$, with the difference in the thermodynamic potentials of two states, one of which is time-dependent and the other being stationary.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information describes simulation and analysis protocols, including numerical considerations regarding the implementation of the proposed approach. We examine the behavior of the proposed diffusion estimator when a temporal memory is added to the diffusive (velocity) fluctuations and when stochastic correlations exist across population members. We further demonstrate the proposed procedure on the relaxation of a system for a corrugated landscape. This material is available free of charge via the Internet at http://pubs.acs.org.

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**Notes**

The authors declare no competing financial interest.

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