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Monte Carlo Sampling in Path Space: Calculating Time Correlation Functions by Transforming Ensembles of Trajectories

Christoph Dellago[*] and Phillip L. Geissler[†]

[*]*Institute for Experimental Physics, University of Vienna, Boltzmanngasse 5, 1090 Vienna, Austria*
[†]*Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139*

Abstract. Computational studies of processes in complex systems with metastable states are often complicated by a wide separation of time scales. Such processes can be studied with transition path sampling, a computational methodology based on an importance sampling of reactive trajectories capable of bridging this time scale gap. Within this perspective, ensembles of trajectories are sampled and manipulated in close analogy to standard techniques of statistical mechanics. In particular, the population time correlation functions appearing in the expressions for transition rate constants can be written in terms of free energy differences between ensembles of trajectories. Here we calculate such free energy differences with thermodynamic integration, which, in effect, corresponds to reversibly changing between ensembles of trajectories.

INTRODUCTION

Transition path sampling is a computational technique developed by us and others to study rare events in complex systems [1, 2, 3]. Although rare, such events are crucially important in many condensed matter systems. Nucleation of first order phase transitions, transport in solids, chemical reactions in solution, and protein folding all occur on time scales which are long compared to basic molecular motions. Transition path sampling, which is based on an importance sampling in trajectory space, can provide insights into mechanism and kinetics of processes involving dynamical bottlenecks. In the following we will give a brief overview of this methodology, focusing on the calculation of reaction rate constants. In this framework reaction rates are related to the reversible work required to manipulate ensembles of trajectories. As a consequence, rate constants can be calculated using free energy estimation methods familiar from equilibrium statistical mechanics, such as umbrella sampling and thermodynamic integration. For an in depth treatment of all aspects of transition path sampling we refer the reader to the review articles [2] and [3].

In the path sampling approach dynamical pathways of length t are represented by ordered sequences of $L = t/\Delta t + 1$ states, $x(t) \equiv \{x_0, x_{\Delta t}, x_{2\Delta t}, \ldots, x_t\}$. Consecutive states are separated by a time increment Δt. Such dynamical pathways can be deterministic trajectories as generated by Newtonian dynamics or stochastic trajectories as constructed from Langevin dynamics or from Monte Carlo simulations. For Markovian single step transition probabilities $p(x_{i\Delta t} \to x_{(i+1)\Delta t})$ the statistical weight $\mathcal{P}[x(t)]$ of a particular

trajectory $x(t)$ is

$$\mathcal{P}[x(t)] = \rho(x_0) \prod_{i=0}^{L-1} p(x_{i\Delta t} \to x_{(i+1)\Delta t}), \tag{1}$$

where $\rho(x_0)$ is the distribution of initial states x_0. In many applications, $\rho(x_0)$ will be an equilibrium distribution such as the canonical distribution, but non-equilibrium distributions of initial conditions are possible as well.

In applying transition path sampling one is usually interested in finding dynamical pathways connecting stable (or metastable) states, which we name A and B. Then, the probability of a *reactive* pathway, i.e., of a pathway starting in A and ending in B, is

$$\mathcal{P}_{AB}[x(t)] \equiv h_A(x_0)\mathcal{P}[x(t)]h_B(x_t)/Z_{AB}(t), \tag{2}$$

where $h_A(x)$ and $h_B(x)$ are the population functions for regions A and B. That is, $h_A(x)$ is 1 if x is in A and 0 otherwise, and $h_B(x)$ is defined analogously. The factor Z_{AB},

$$Z_{AB}(t) \equiv \int \mathcal{D}x(t)\, h_A(x_0)\mathcal{P}[x(t)]h_B(x_t), \tag{3}$$

normalizes the reactive path probability, and the notation $\int \mathcal{D}x(t)$ indicates an integration over all time slices of the pathway. The quantity $Z_{AB}(t)$ can be viewed as a partition function characterizing the ensemble of all reactive pathways. This analogy between conventional equilibrium statistical mechanics and the statistics of trajectories will be important in the discussion of reaction kinetics in the next section. The distribution $\mathcal{P}_{AB}[x(t)]$, which weights trajectories in the *transition path ensemble*, is a statistical description of all dynamical pathways connecting regions A and B.

To sample the transition path ensemble we have developed several Monte Carlo simulation techniques [4, 5]. In these algorithms, which are importance sampling procedures in trajectory space, one proceeds by generating trial pathways from existing trajectories via what we call the shooting and shifting method [4]. Newly generated trial pathways are then accepted with a probability obeying the detailed balance condition. This condition guarantees that pathways are sampled according to their weight in the transition path ensemble. The detailed balance condition can be satisfied by choosing an acceptance probability according to the celebrated Metropolis rule [6]. Using such an acceptance probability in conjunction with the shooting and shifting algorithms one can efficiently explore trajectory space and harvest reactive pathways with their proper weight. Statistical analysis of the harvested pathways can then provide information on the kinetics of transition. The basis for this type of analysis will be discussed in the following section.

REACTION RATES

The time correlation function of state populations

$$C(t) \equiv \frac{\langle h_A(x_0)h_B(x_t)\rangle}{\langle h_A(x_0)\rangle} \tag{4}$$

provides a link between the microscopic dynamics of the system and the phenomenological description of the kinetics in terms of the forward and backward reaction rate constants k_{AB} and k_{BA}, respectively [7]. If the reaction time $\tau_{\text{rxn}} = (k_{AB} + k_{BA})^{-1}$ is significantly larger than the time τ_{mol} necessary to cross the barrier top, $C(t)$ approaches its long time value exponentially after the short molecular transient time τ_{mol}:

$$C(t) \approx \langle h_B \rangle (1 - \exp\{-t/\tau_{\text{rxn}}\}), \tag{5}$$

For $\tau_{\text{mol}} < t \ll \tau_{\text{rxn}}$ the population correlation function $C(t)$ grows linearly:

$$C(t) \approx k_{AB}t. \tag{6}$$

Thus, the forward reaction rate constant can be determined from the slope of $C(t)$ in this time regime.

To evaluate $C(t)$ in the transition path sampling framework we rewrite it in terms of sums over trajectories:

$$C(t) = \frac{\int \mathcal{D}x(t)\, h_A(x_0)\mathcal{P}[x(t)]h_B(x_t)}{\int \mathcal{D}x(t)\, h_A(x_0)\mathcal{P}[x(t)]} = \frac{Z_{AB}(t)}{Z_A}. \tag{7}$$

The above expression can be viewed as the ratio between the "partition functions" for two different path ensembles: one, Z_A, in which pathways start in A and end anywhere, and one, $Z_{AB}(t)$, in which pathways start in A and end in B. This perspective suggests that we determine the correlation function $C(t)$ via calculation of $\Delta F(t) \equiv F_{AB}(t) - F_A = -\ln Z_{AB}(t) + \ln Z_A$, in effect a difference of free energies. From the free energy difference one can than immediately determine the time correlation function, $C(t) = \exp[-\Delta F(t)]$. The free energy difference $\Delta F(t)$ can be viewed as the work necessary to reversibly change from a path ensemble with free final points x_t to a path ensemble in which the final points x_t are required to reside in region B.

In principle, one can determine the reaction rate constant k_{AB} by calculating the time correlation function $C(t)$ at various times and by taking a numerical derivative with respect to t. This procedure is, however, numerically costly since it requires repeated free energy calculations. Fortunately, the reversible work $\Delta F(t')$ for a given time t' can be written as a sum of the reversible work $\Delta F(t)$ for a different time t and the reversible work $F(t',t)$ necessary to change t to t' [2]:

$$\Delta F(t') = \Delta F(t) + F(t',t). \tag{8}$$

This reversible work $F(t',t)$ can then be calculated for all times between 0 and t' in a single transition path sampling simulation, as described in detail in Ref. [2]. In the following sections we will focus on ways to determine the reversible work $\Delta F(t)$ for a single time t.

MODEL

To illustrate the numerical methods presented in this paper we have used them to calculate the time correlation function $C(t)$ for isomerizations occurring in a simple

diatomic molecule immersed in a bath of purely repulsive particles, schematically shown on the left hand side panel of Fig. 1. A very similar model has been studied by Straub, Borkovec, and Berne [8]. This two dimensional model consists of N point particles of unit mass interacting via the Weeks-Chandler-Anderson potential [9],

$$V_{\text{WCA}}(r) = \begin{cases} 4\varepsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^{6} \right] + \varepsilon & \text{for} \quad r \leq r_{\text{WCA}} \equiv 2^{1/6}\sigma, \\ 0 & \text{for} \quad r > r_{\text{WCA}}. \end{cases} \qquad (9)$$

Here, r is the interparticle distance, and ε and σ specify the strength and the interaction radius of the potential, respectively. In addition, two of the N particles are bound to each other by a double well potential

$$V_{\text{dw}}(r) = h \left[1 - \frac{(r - r_{\text{WCA}} - w)^2}{w^2} \right]^2, \qquad (10)$$

where h denotes the height of the potential energy barrier separating the potential energy wells located at $r_{\text{WCA}} = 2^{1/6}\sigma$ and $r_{\text{WCA}} + w$.
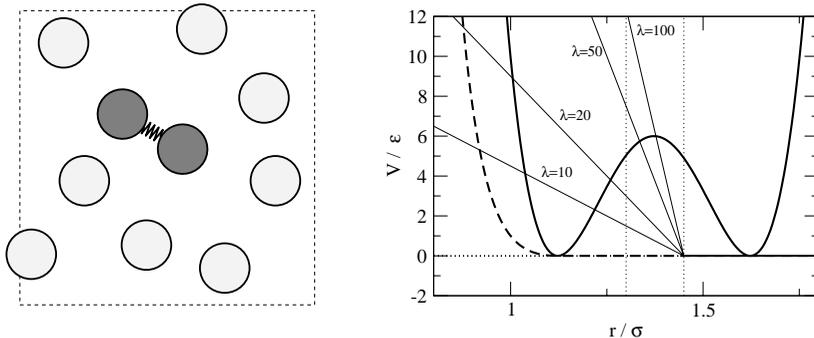

FIGURE 1. (a) Schematic representation of the diatomic molecule (dark grey disks) held together by a spring immersed in the WCA fluid (light grey disks). (b) Intramolecular (solid line) and intermolecular (dashed line) potential energy. The parameters determining height and width of the double well potential are $h = 6\varepsilon$ and $w = 0.5\sigma$. The thin lines denote the "drawbridge" constraining potential used in the thermodynamic integration and are labelled from $\lambda = 10$ to $\lambda = 100$ according to their slopes. The limits r_A and r_B for states A and B, respectively, are shown as vertical dotted lines.

The diatomic molecule held together by the potential shown in Fig. 1 can reside in two states. In the *contracted* state the interatomic distance r fluctuates around r_{WCA}, while in the *expanded* state r is close to $r_{\text{WCA}} + w$. Due to interactions with the solvent particles, transitions between the two states can occur provided the total energy of the system is sufficiently high. Collisions with solvent particles provide the energy for activation as well as the dissipation necessary to stabilize the molecule in one of the wells after a barrier crossing has occurred. For high barriers, transitions between the extended and the contracted state are rare. In all calculations the system is defined to be in state A if the interatomic distance $r < r_A = 1.35\sigma$ and in state B if $r > r_B = 1.45\sigma$. These limiting values are denoted by vertical dotted lines in the right hand side panel of Fig. 1. The

Newtonian equations of motion are integrated with the velocity Verlet algorithm [10] using a time step of $\Delta t = 0.002(m\sigma^2/\varepsilon)^{1/2}$.

THERMODYNAMIC INTEGRATION

In Ref. [4] we determined the time correlation function $C(t)$ with an umbrella sampling approach. Here we show how the time correlation function $C(t)$ from Equ. (7) can be calculated with a strategy analogous to thermodynamic integration, a method used to estimate the free energy difference between ensembles [11, 12]. In a conventional thermodynamic integration, one introduces a coupling parameter λ, which can transform one ensemble into the other when changed from λ_i to λ_f. Derivatives of the free energy with respect to λ calculated at intermediate values of λ can then be used to compute the free energy difference by numerical integration from λ_i to λ_f.

Thermodynamic integration can also be used to calculate free energy differences between path ensembles. Such a strategy has in effect been used by S. Sun [13] to efficiently estimate free energy difference in the fast switching method recently proposed by Jarzynski [14, 15, 16, 17, 18]. For our purpose we introduce a function $\Theta(x,\lambda)$ depending on the configuration x and on a parameter λ. The dependence on λ is chosen such that $\Theta(x,\lambda_i) = 1$ and $\Theta(x,\lambda_f) = h_B(x)$. Using this function Θ one can then continuously transform an ensemble of paths starting in A and ending anywhere into an ensemble of pathways beginning in A and ending in B.

Introducing the partition function

$$Z(t,\lambda) \equiv \int \mathcal{D}x(t)\, h_A(x_0) \mathcal{P}[x(t)] \Theta(x_t,\lambda) \tag{11}$$

we generalize the time correlation function $C(t)$ from Equ. (7) as the ratio between partition functions for λ and λ_i:

$$C(t,\lambda) = Z(t,\lambda)/Z(t,\lambda_i). \tag{12}$$

For $\lambda = \lambda_f$ this function is just the correlation function $C(t) = \exp(-\Delta F)$ we wish to determine. We calculate the reversible work $F(t,\lambda) \equiv -\ln Z(t,\lambda)$ by first taking its derivative with respect to λ:

$$\frac{\partial F(t,\lambda)}{\partial \lambda} = -\frac{\partial \ln Z(t,\lambda)}{\partial \lambda} = -\frac{1}{Z(t,\lambda)}\frac{\partial}{\partial \lambda} Z(t,\lambda). \tag{13}$$

Using the definition of Z we obtain

$$\frac{\partial F(t,\lambda)}{\partial \lambda} = -\int \mathcal{D}x(t)\, h_A(x_0) \mathcal{P}[x(t)] \frac{\partial \Theta(x_t,\lambda)}{\partial \lambda} / Z(t,\lambda). \tag{14}$$

To bring this expression into a form amenable to a path sampling simulation we define an "energy" $U(x,\lambda)$ related to the function Θ by:

$$U(x,\lambda) \equiv -\ln \Theta(x,\lambda). \tag{15}$$

Inserting the above expression into Equ. (14) we finally obtain:

$$\frac{\partial F(t,\lambda)}{\partial \lambda} = \frac{1}{Z(t,\lambda)} \int \mathcal{D}x(t)\, h_A(x_0) \mathcal{P}[x(t)]\Theta(x_t,\lambda) \frac{\partial U(x_t,\lambda)}{\partial \lambda} = \left\langle \frac{\partial U(x_t,\lambda)}{\partial \lambda} \right\rangle_\lambda. \quad (16)$$

Here, $\langle \cdots \rangle_\lambda$ denotes a path average carried out in the ensemble described by

$$\mathcal{P}[x(t),\lambda] \equiv h_A(x_0)\mathcal{P}[x(t)]\Theta(x_t,\lambda)/Z(t,\lambda). \quad (17)$$

This is the ensemble of all pathways starting in region A with a bias $\Theta(x_t,\lambda)$ acting on x_t, the last time slice of the pathway. The biasing function $\Theta(x,\lambda)$ is designed to pull the path endpoints gradually towards region B as λ is increased and to finally confine them to region B for $\lambda = \lambda_f$. From derivatives $\partial F(t,\lambda)/\partial \lambda$ computed for several values of λ in the range between λ_i and λ_f one then can calculate the reversible work $\Delta F(t) = F(t,\lambda_f) - F(t,\lambda_i)$ by integration:

$$\Delta F(t) = \int_{\lambda_i}^{\lambda_f} d\lambda \left\langle \frac{\partial U(x_t,\lambda)}{\partial \lambda} \right\rangle_\lambda. \quad (18)$$

The correlation function we originally set out to compute is then simply given by $C(t) = \exp[-\Delta F(t)]$.

To study transitions of our solvated diatomic molecule, we introduce a "drawbridge" potential anchored at r_B:

$$U(x,\lambda) \equiv \lambda \times [r_B - r(x)] \times \theta[r_B - r(x)]. \quad (19)$$

Here, r_B is the lower limit of r in region B and θ is the Heaviside theta function. By lifting the drawbridge from $\lambda = 0$ to $\lambda = \infty$ one can continuously confine the initially free endpoints of the pathways to final region B. For this drawbridge biasing potential the derivative of the reversible work $F(t,\lambda)$ is given by

$$\frac{\partial F(t,\lambda)}{\partial \lambda} = \langle [r_B - r(x_t)] \times \theta[r_B - r(x_t)]\rangle_\lambda. \quad (20)$$

We have used Equ. (20) to calculate $\partial F(t,\lambda)/\partial \lambda$ for $t = 0.8(m\sigma^2/\varepsilon)^{1/2}$ at 100 equidistant values of λ in the range from $\lambda = 0$ to $\lambda = 100$. Each single path sampling simulation consisted of 2×10^6 attempted path moves. In this sequence of path sampling simulations starting at $\lambda = 0$ and ending at $\lambda = 100$, corresponding to a *compression* of pathways, the final path of simulation n was used as initial path for simulation $n+1$. Results of these simulations are plotted in Fig. 2. Derivatives of the reversible work with respect to λ are shown on the left hand side. The right panel contains the reversible work $F(t,\lambda)$ as a function of λ as obtained by numerical integration. The plateau value of $F(t,\lambda) = 9.85$ reached at $\lambda \sim 40$ is the reversible work $\Delta F(t)$ necessary to confine the final points of the pathways to region B. To investigate if these results are affected by hysteresis, we have carried out a sequence of path sampling simulations corresponding to an *expansion* of the path ensemble. In this sequence of simulations we started with pathways constrained to end in region B end then subsequently lowered λ from an initial value of 100
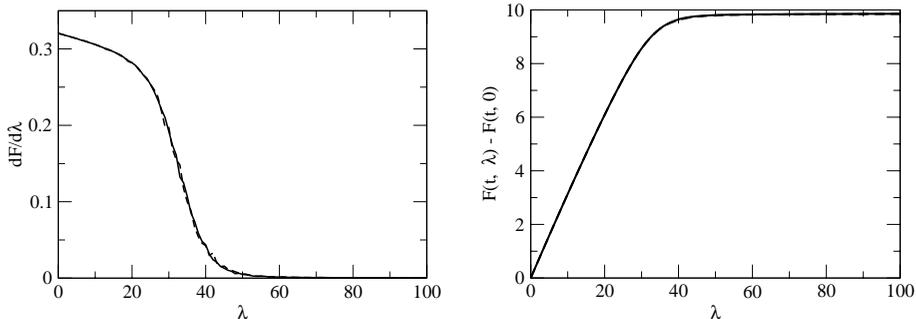
FIGURE 2. Results of path ensemble thermodynamic integration simulations. Left hand side: derivatives of the reversible work $F(t, \lambda)$ with respect to the coupling parameter λ calculated in a path compression simulation (solid line) and in a path expansion simulation (dashed line). In both cases $\partial F / \partial \lambda$ was calculated at 101 equidistant values of λ in the range from 0 to 100. Right hand side: Reversible work $F(t, \lambda)$ as a function of λ obtained by numerical integration of the curves shown on the left hand side. Again, the solid line denotes results of a path ensemble compression while the dashed line refers to a path ensemble expansion. The free energy difference obtained from these simulations is $\Delta F(t) = 9.85$ corresponding to a correlation function value of $C(t) = 5.27 \times 10^{-5}$.

to a final value of 0. The reversible work and its derivative obtained by path expansions are shown as dashed lines in Fig. 2. Path compression and path expansion yield almost identical results.

In this work we have borrowed many familiar ideas and techniques from statistical thermodynamics (e.g., reversible work, thermodynamc integration) in order to compute intrinsically dynamical quantities (e.g., rate constants). Thermodynamic concepts become directly useful for this purpose once the dynamical problem has been reduced to characterizing the statistical consequences of imposing constraints (of reactivity) on stationary distributions (of dynamical pathways). This task, in the context of phase space ensembles, is the central challenge of classical statistical mechanics. Remarkably, such a thermodynamic interpretation extends even to the nonequlibrium realm. Recent results concerning *irreversible* transformations between equilibrium states [14, 15, 16, 17, 18] have analogous meaning for finite-time switching between ensembles of trajectories, opening new routes for rate constant calculations. We are working to develop transition path sampling methods exploiting this analogy.

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