Activation energies by molecular dynamics with constraints

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Recently Tobias and Broods introduced a method to compute by molecular dynamics with constraints the probability density $P(r) = \langle \delta(r-f) \rangle$ associated with rate values $f$ of a spatial coordinate $r$. In this Letter we extend their approach to the case of a general reaction coordinate $\xi(r)$, an arbitrary function of the configuration-space coordinates. The generalized version is shown to be the integral form of the free energy calculation in the constrained-reaction-coordinate ensemble where the mean force is computed as an average in a $\xi$-constrained ensemble. The two approaches are shown to be of equal computational efficiency for a very simple Lennard-Jones test case.

1. Introduction

An activated process is a transition between stable states separated by a region of low probability and can often be viewed as the crossing of a free energy barrier. Considerable effort has been devoted to molecular dynamics (MD) simulations of activated processes. (For references to recent MD studies of activated processes see, for instance, ref. [11]—[1].) If the free energy barrier is much higher than $k_B T$, barrier crossing is an infrequent event which cannot be simulated by conventional techniques. If the transition process can be described by a phenomenological rate equation, then the associated rate constants can be calculated within the reactive-flux correlation-function formalism [2]. It is convenient to express the rate constant as the product of two terms: a static part (transition-state-theory rate constant) which is proportional to the probability of finding the system at the barrier maximum, or more generally at the dividing surface in phase space that separates the reactant and product regions, and a dynamical correction (transmission coefficient) which accounts for recrossing the dividing surface. The transmission coefficient can be calculated with little computational effort from trajectories originating at the barrier maximum. One of the most computationally challenging tasks is the calculation of the probability of finding the system at the barrier maximum.

Transitions between stable states in a many-body dynamical system often can be described in terms of a classical reaction coordinate $\xi(r)$, where $r$ represents the set of coordinates of all the degrees of freedom of the system. The quantity $\xi$ can be thought of as a parameter that takes on a fixed set of values as the system moves from one stable state to the other; all other degrees of freedom are free to relax during this process. Some attention should be paid to the choice of the reaction coordinate (see, for example, ref. [3]) since in general $\xi(r)$ can be a complicated function of all the coordinates of the system.
The probability density to find the system at any point of configuration space for a prescribed value $\zeta_1$ of $\zeta(r)$ is

$$P(\zeta(r) = \zeta_1) = \langle \delta(\zeta(r) - \zeta_1) \rangle = C \exp[-\beta W(\zeta_1)],$$

where $\beta = 1/k_B T$, $\langle \cdot \rangle$ is the canonical-ensemble average and the last equality defines the potential of mean force $W(\zeta)$ associated with the reaction coordinate. The difference $W(\zeta_1) - W(\zeta_2)$ is the reversible work needed to take the system from some reference value $\zeta_2$ of $\zeta(r)$ to $\zeta_1$. The constant $C$ is determined by the normalization condition on $P(\zeta)$. If $\zeta'$ is a local maximum for $W(\zeta)$ we can identify the hypersurface $\zeta(r) = \zeta'$ as the dividing surface; thus, $P(\zeta')$ is the quantity of interest. Of course, direct methods cannot be used to determine this quantity since $\zeta'$ is a highly improbable value of $\zeta$.

A number of methods have been proposed to solve this difficult sampling problem. Perhaps the best-known method for computing quantities like $P(\zeta)$ is umbrella sampling [4]. In this method, a biased sampling is introduced that favors improbable values of $\zeta$, and the probability density $P(\zeta)$ can be computed by introducing a suitable weight factor to correct for the biased sampling. Often more than one biasing function is needed to sample efficiently for the entire range of $\zeta$, and in this case an integration must be performed to obtain the quantity of interest. Another method is that of ref. [5] ("blue moon" ensemble) in which the mean force on $\zeta, F(\zeta) = -dW(\zeta)/d\zeta$, is defined and written in a form that lends itself to computation by a $\zeta$-constrained MD simulation [6]. Yet another approach is that of Tobias and Brooks [7] where $W(\zeta)$ is calculated using a difference method.

In this Letter, we present a generalization of the method of Tobias and Brooks and compare the results with those of the "blue moon" ensemble. In their original formulation, Tobias and Brooks restrict $\xi$ to be a coordinate of the system (their approach is still applicable if $\xi$ is a linear function of the coordinates). The present formulation allows $\xi$ to be an arbitrary function $\xi(r)$ of the configuration-space coordinates, and we show that this generalization is simply the integral form of the "blue moon" ensemble.

In section 2, we derive the main result for a simple atomic system while in the appendix we give the corresponding formulas for the case of a molecular system with some intramolecular degrees of freedom frozen by rigid constraints. In section 3, we show that the approach of Tobias and Brooks has the same numerical efficiency as that of the "blue moon" method in the simple case in which $\xi$ is the relative distance of two Lennard-Jones (LJ) particles in a LJ fluid.

### 2. General formulation and computational method

We consider a system composed of $N$ atoms with masses $m_i$ ($i = 1, \ldots, N$) with the configuration space given by $3N$ Cartesian coordinates $r = (r_1, r_2, \ldots, r_N)$. As in ref. [7], we notice that the difference of the potential of mean force for two values of $\zeta(r)$, $\zeta_1$ and $\zeta_2$, is given by

$$W(\zeta_1) - W(\zeta_2) = -k_B T \ln \frac{P(\zeta(r) = \zeta_1)}{P(\zeta(r) = \zeta_2)} = -k_B T \ln \left[ \int \exp[-\beta V(r)] \delta(\zeta(r) - \zeta_1) \right] - \left[ \int \exp[-\beta V(r)] \delta(\zeta(r) - \zeta_2) \right].$$

(2)

where $u = (\xi, q)$ is a set of generalized coordinates with $q = (q_1, q_2, \ldots, q_{3N-1})$ and $|J| = \partial r/\partial u$ is the Jacobian of the canonical transformation $\{r\} \rightarrow \{u\}$; the quantity $V'(u)$ is $V(r(u))$ with $V(r)$ the potential energy of the system.

In view of the presence of the delta function, the integral over $\xi$ in the numerator of eq. (2), is easily performed and only an integral over $q$ remains. Multiplying the integral by $\int d\xi \exp[-\beta V'(\zeta_1, q)] \exp[\beta V'(\zeta, q)]$
\( q \) \( \delta (\zeta - \zeta_0) \), i.e. by 1, we can rewrite the numerator as an integral over the entire set of generalized coordinates \( u \),

\[
W(\zeta_1) - W(\zeta_2) = -k_B T \ln \left[ \frac{\int dq |J(\zeta_1, q)| \exp \left\{ -\beta \left[ V(\zeta_1, q) - V(\zeta_2, q) \right] \right\} \exp \left\{ -\beta V''(u) \right\} \delta(\zeta - \zeta_2)}{\int dr \exp \left\{ -\beta V(r) \right\} \delta(\zeta(r) - \zeta_2)} \right]
\]

\[
= -k_B T \ln \frac{\langle J^{-1} | J_{\zeta} | \exp(-\beta \Delta V) \delta(\zeta(r) - \zeta_2) \rangle}{\langle \delta(\zeta(r) - \zeta_2) \rangle},
\]

where the configurational canonical-ensemble average is

\[
\langle \rangle = \frac{1}{Q} \int dr \cdots \exp\left[ -\beta V(r) \right] = \frac{1}{Q} \int dq |J| \cdots \exp\left[ -\beta V(u) \right].
\]

Eq. (3) is the sought-for generalization and should be compared with eq. (6) of ref. [7] which does not contain the Jacobian factors. Some comments are in order to clarify the meaning of the numerator of the logarithmic argument in eq. (3). In dynamical terms, it can be viewed as an average over a trajectory in the configuration space in which only points with \( \zeta(r) = \zeta_2 \) contribute. For each of these points, \( \Delta V = V(\zeta_1, q(r)) - V(\zeta_2, q(r)) \) \( = V_{\zeta}(r) - V_{\zeta_2}(r) \). Here, \( V_{\zeta}(r) \) and \( |J_{\zeta}| \) are the values of \( V \) and \( |J| \) at a point that is the projection on the hypersurface \( \zeta(r) = \zeta_2 \) of a given point on the trajectory. The quantity \( V_{\zeta_2}(r) \) is the value of \( V \) corresponding to the hypersurface \( \zeta(r) = \zeta_2 \).

Eq. (3) can be directly calculated with constrained-reaction-coordinate dynamics. In fact, it has been shown in ref. [5] that the conditional average at \( \zeta \) of an observable \( O(r) \) can be obtained as the weighted average of \( O \) over a dynamics with the constraint \( \zeta = \zeta_2 \) imposed,

\[
\langle O(r) | \delta(\zeta(r) - \zeta_2) \rangle = \frac{\langle |Z|^{-1/2} O(r) \rangle_{\zeta_2}}{\langle |Z|^{-1/2} \rangle_{\zeta_2}},
\]

where \( Z = \sum_{n} m_{\zeta}^{-1} |\partial \zeta / \partial r|^{2} \). Eq. (4) is derived in ref. [5]. The factor \( Z^{-1/2} \) is a bias arising from the fact that during the calculation of \( \langle \rangle_{\zeta_2} \), the system is overconstrained since the momentum associated with \( \zeta \) is constrained \(^{11} \). Finally, we have

\[
W(\zeta_1) - W(\zeta_2) = -k_B T \ln \frac{\langle J^{-1} | J_{\zeta} | \exp(-\beta \Delta V) \rangle_{\zeta_2}}{\langle |Z|^{-1/2} \rangle_{\zeta_2}}.
\]

To evaluate the expression on the right-hand side of eq. (5), a constant-temperature constrained molecular dynamics can be carried out using standard methods [8,9]. At each time step, the quantities \( V_{\zeta_2}(r) \) and \( |J_{\zeta}| \) must be calculated as described above. Next, we observe that the derivative of eq. (3) corresponds to the expression for the mean force given in ref. [5]. On taking \( \zeta_2 \) as a fixed references point and differentiating expression (3) with respect to \( \zeta_1 \), we obtain

\[
F(\zeta_1) = -\frac{d}{d\zeta_1} W(\zeta_1) = -\frac{d}{d\zeta_1} [W(\zeta_1) - W(\zeta_2)] = k_B T \left[ \frac{\int dq |J(\zeta_1, q)| \exp \left\{ -\beta V(\zeta_1, q) \right\} \exp \left\{ -\beta V''(u) \right\} \delta(\zeta - \zeta_2)}{\int dq |J(\zeta_1, q)| \exp \left\{ -\beta V''(u) \right\} \delta(\zeta - \zeta_2)} \right]
\]

\[
= k_B T \left[ \frac{\int du \exp \left\{ -\beta V''(u) \right\} \left\{ \partial J(u) / \partial \zeta - \partial J(u) / \partial \zeta \right\} \delta(\zeta - \zeta_2)}{\int du |J(u)| \exp \left\{ -\beta V''(u) \right\} \delta(\zeta - \zeta_2)} \right]
\]

\[
= \frac{\langle \delta \zeta / \partial \zeta \rangle \left\{ -\delta V / \partial \zeta + \beta^{-1} \langle \delta \ln |J| / \partial r \rangle \delta(\zeta(r) - \zeta_2) \right\}}{\langle \delta(\zeta(r) - \zeta_2) \rangle}.
\]

\(^{11} \) Although \( Z \) is a scalar for this simple case where there are no additional constraints, it is in general a matrix if other constraints are present; for example, if bond lengths or angles are fixed. We use the boldface symbol whenever the \( \zeta \) constraint is present in order to distinguish it from the \( Z \) factor introduced in the appendix.
This expression is identical to that of ref. [51] for the mean force in a system with no molecular constraints. In the appendix, we give the generalizations of eqs. (3) and (6) when the molecular internal degrees of freedom are modelled by a number of rigid constraints between the atoms constituting the molecules.

Eq. (3) is valid for every pair of values $\zeta_1$, $\zeta_2$. However, if $\zeta_1$ is far from $\zeta_2$, the factor $\exp(-\beta\Delta V)$ can be vanishingly small and the sampling needed to estimate the expectation value will be difficult; thus, eq. (3) can be used only to compute the difference between the potential of mean force for two nearby values of the reaction coordinate $\zeta$. However, eq. (6) gives for each value of $\zeta$ the absolute value of the mean force acting on $\zeta$. The potential of mean force can be obtained by integrating the force function. To do this, the force must be known on a set of closely separated $\zeta$ values. If we take $\zeta_2=\zeta$ and $\zeta_1=\zeta \pm \delta \zeta$ in eq. (3) and $\zeta_1=\zeta$ in eq. (6), it is obvious that eqs. (3) and (6) for $\delta \zeta \to 0$ yield the same information about $W(\zeta)$.

3. An application and numerical test

Perhaps the simplest test of the two methods described above is the evaluation of the potential of mean force between two tagged atoms in a simple system like liquid argon. Indeed, this is the application discussed in ref. [7]. Here, we use it to check the relative efficiency of the two approaches.

We take $\zeta=r_1-r_2$ as our reaction coordinate, where $r_1$ and $r_2$ are the coordinates of the two tagged atoms, and take as complementary generalized coordinates the two angles $(\theta, \phi)$ which arise from the expression for $r_1-r_2$ in spherical polar coordinates, the three Cartesian coordinates of the centre-of-mass of particles 1 and 2 and the $3N-6$ Cartesian coordinates of the other particles. In this case, $|J|=r^2 \cos \phi$ and $Z=2/m$ (where $m$ is the mass of a particle). Then from eq. (5),

$$W(r+\delta r) - W(r) = -k_B T \ln \left( \frac{(r+\delta r)^2}{r^2} \exp(-\beta\Delta V) \right) = -k_B T \ln \langle \exp(-\beta\Delta V) \rangle, \quad -2k_B T \ln \langle \frac{r+\delta r}{r} \rangle. \quad (7)$$

The last equality follows from the fact that the ratio of Jacobians in eq. (5) in this particular case factors out of the statistical average because it happens to be $\zeta$-independent. The last factor is proportional to the apparent (centrifugal) force on the $r$ variable (see ref. [10]).

A comment is in order on the symbols used in eq. (7) and in ref. [7]. For a homogeneous and isotropic system like liquid argon enclosed in a volume $V$, there is a simple relation between the radial distribution function and the probability density $P$ of finding two tagged atoms at distance $r$. $(4\pi/V)r^2g(r)=P(|r_1-r_2|=r)$.

Therefore,

$$P(|r_1-r_2|=r+\delta r) = \frac{(r+\delta r)^2}{r^2} \langle \exp(-\beta\Delta V) \rangle, \quad \text{and}$$

$$g(r+\delta r) = \frac{\langle \exp(-\beta\Delta V) \rangle}{r^2}. \quad (8)$$

Eq. (8) is what Tobias and Brooks computed in ref. [7]. However, it must be noted that the function $W(r)$ in eq. (7) and fig. 1 does not have the same meaning as that of ref. [7], where the centrifugal term is missing.

An analogous simplification is found in the expression for the mean force. From eqs. (6) and (4), we have

$$F(r) = \langle -\frac{\partial V}{\partial r} \rangle + \frac{2}{\beta r}. \quad (9)$$

The model used in our test is the same as in ref. [7], namely 108 Lennard-Jones atoms at density $\rho=0.7967$ and temperature $T=0.7179$ representing argon in the liquid phase near the triple point (we use LJ reduced
units with $\sigma = 3.405 \text{ Å}$, $\epsilon/k_B = 119.8 \text{ K}$, $m = 1$) with periodic boundary conditions and the potential truncated at $r_c = 2.5\sigma$. The potential of mean force was calculated from 32 simulations where the two tagged atoms are constrained at distances that range from 0.950 to 2.500 in increments of 0.05$\sigma$. The time step used to integrate the equations of motion was $0.005(m\sigma^2/\epsilon)^{1/2}$ corresponding roughly to $10^{-2}$ ps. In each simulation, both the mean force $F(r)$ and the differences $W(r+0.025) - W(r)$, $W(r-0.025) - W(r)$ were calculated from averages over 40000 time steps. The potential of mean force can be calculated only within an additive constant that we fix by taking $W(r_c) = 0$. The reference curve (solid curve in fig. 1) for $W(r)$ was obtained computing directly the probability $P(\mid r_1 - r_2 \mid = r) = N(N-1)P(\mid r_1 - r_2 \mid = r)$, i.e. $g(r)$, from a 7 ns run (the reference curve for $F(r)$ was obtained by numerically differentiating $W(r)$). Fig. 1 shows plots of $W(r)$ obtained from eq. (7) and $F(r)$ obtained independently from eq. (9). The comparison between the two methods was made both by integrating $F(r)$ and differentiating $W(r)$. The results are overlapping and the statistical error is also the same. Reported errors on $W(r)$ and $F(r)$ were estimated (in both methods) by evaluating the standard deviation on a set of 20 segments, each 2000 time steps long. We conclude that the two methods are equivalent in computational efficiency for this simple case. However, it is not obvious if this equivalence persists for other cases where $\xi(r)$ is a general nonlinear function of all coordinates. For a general nonlinear reaction coordinate the Jacobian determinant may be complex and in general will not factor out of the ensemble average. Since the Jacobian enters in the ensemble average in different ways in the two methods their relative efficiencies may vary depending on the choice of reaction coordinates.

The results presented in this paper show how the mean force and potential of mean force corresponding to an arbitrary function $\xi(r)$ of all the configurational coordinates of the system can be computed using $\xi$-constrained molecular dynamics. Thus, the techniques described here should be applicable to a variety of problems involving activation barriers, such as classical and quantum reaction rates and diffusion in solids.
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Appendix

If the dynamic properties of molecules are studied over time scales much longer than the times that characterize intramolecular vibrations, it is possible to freeze out the vibrational degrees of freedom by imposing rigid constraints. Consider rigid or partly rigid molecules where \( l \) constraint relations are imposed between the atomic positions. Such relations can always be written in the form

\[ \sigma_{\alpha}^{k} = \sigma_{\alpha}^{k}(r_{\alpha}) = 0, \quad \text{(10)} \]

and imply

\[ \dot{\sigma}_{\alpha}^{k} = \dot{\sigma}_{\alpha}^{k}(r_{\alpha}, p_{\alpha}) = 0, \]

where \( \alpha \) labels the molecules, \( k (k = 1, \ldots, L) \) is the constraint label and \( r_{\alpha} \) is the set of coordinates of the "components" of molecule \( \alpha \). In the simplest case, the components of a molecule are atoms constrained in pairs with rigid bonds to form a system of diatomic molecules. To carry out statistical mechanics calculations, one needs to know the dynamics of the constrained system, which can be naturally obtained via the Lagrangian formalism. However, it is possible to carry out the computation in terms of the original Cartesian atomic coordinates and obtain an explicit expression for the probability measure of the constrained system. Suppose that \( N \) atoms with masses \( m_{i} (i = 1, \ldots, N) \) and Cartesian coordinates \( r = (r_{1}, r_{2}, \ldots, r_{N}) \) form a system of \( M \) molecules through \( Ml \) holonomic constraints \( \sigma_{\alpha}^{k}(r_{\alpha}) = 0 (\alpha = 1, \ldots, M; k = 1, \ldots, l) \). To simplify the notation, we let \( L = Ml \) and label constraints by the index \( j \), \( \sigma_{j}(r) = 0 (j = 1, \ldots, L) \), where the dependence of each constraint on the subject of coordinates has not been specified. It can be shown [9] that the canonical configurational probability density for such system is

\[ P(r) = \frac{1}{Z_{L}} |Z|^{1/2} \exp(-\beta V) \prod_{j=1}^{L} \delta(\sigma_{j}(r)), \quad \text{(11)} \]

where \( Z \) is a \( L \times L \) matrix with components

\[ Z_{m,n} = \sum_{i=1}^{N} \frac{1}{m_{i}} \frac{\partial \sigma_{m}}{\partial r_{i}} \frac{\partial \sigma_{n}}{\partial r_{i}}, \quad \text{(12)} \]

and \( Z_{L} \) is the canonical partition function of the system with \( L \) constraints such that \( \int dr P(r) = 1 \). The \( |Z| \) factor in eq. (11) comes from the integration over the momenta of the full canonical probability density in phase space.

In the present case, the difference between the potentials of mean force at \( \zeta_{1} \) and \( \zeta_{2} \) is given by

\[ W(\zeta_{1}) - W(\zeta_{2}) = -k_{B} T \ln \frac{\int dr |Z|^{1/2} \exp[-\beta V(r)] \delta(\zeta(r) - \zeta_{1}) \prod_{j=1}^{L} \delta(\sigma_{j}(r))}{\int dr |Z|^{1/2} \exp[-\beta V(r)] \delta(\zeta(r) - \zeta_{2}) \prod_{j=1}^{L} \delta(\sigma_{j}(r))}, \]

\[ = -k_{B} T \ln \frac{\int dr |J||Z|^{1/2} \exp[-\beta V(\mu)] \delta(\zeta - \zeta_{1}) \prod_{j=1}^{L} \delta(\sigma_{j})}{\int dr |Z|^{1/2} \exp[-\beta V(r)] \delta(\zeta(r) - \zeta_{2}) \prod_{j=1}^{L} \delta(\sigma_{j}(r))}, \]

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where now $\mathbf{u} = (\zeta, \sigma, \mathbf{q})$, $\sigma$ is the vector $(\sigma_1, ..., \sigma_L)$ and $\mathbf{q}$ the vector $(q_1, ..., q_{3N-L-1})$. As usual, $|J|$ is the Jacobian of the transformation $\{r\} \leftrightarrow \{\mathbf{u}\}$. Following the same procedure used to obtain eq. (3), we have

$$W(\xi) - W(\xi_1) = -k_B T \ln \frac{\langle |J|^{-1/2} |Z|^{-1/2} |J_\sigma| |Z_\sigma|^{1/2} \exp(-\beta \Delta V) \delta(\mathbf{r}(\mathbf{r}) - \xi_1) \rangle}{\langle \delta(\mathbf{r}(\mathbf{r}) - \xi) \rangle} \quad (13)$$

where the meaning of the configurational canonical-ensemble average of the constrained system is

$$\langle \rangle = \frac{1}{Q_c} \int d\mathbf{r} |Z|^{1/2} ... \exp[-\beta V(\mathbf{r})] \prod_{j=1}^L \delta(\sigma_j(\mathbf{r})) \equiv \frac{1}{Q_c} \int d\mathbf{u} |J| |Z|^{1/2} ... \exp[-\beta V'(\mathbf{u})] \prod_{j=1}^L \delta(\sigma_j) \cdot$$

The generalization of the mean force, eq. (6), now becomes

$$F(\xi) = -\frac{dW(\xi)}{d\xi_1} = \frac{\langle \delta r / \delta \xi \rangle - \delta V / \delta \mathbf{r} + \beta^{-1} (\partial \ln |J| |Z|^{1/2}) / \partial \mathbf{r} \rangle \delta(\mathbf{r}(\mathbf{r}) - \xi_1) \rangle}{\langle \delta(\mathbf{r}(\mathbf{r}) - \xi_1) \rangle} \quad (14)$$

which is just eq. (14) of ref. [5]. As in the atomic case, both eqs. (13) and (15) can be computed [5] using constrained-reaction-coordinate dynamics.

References