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Activation Processes with Memory

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We propose a mathematical treatment of the activated processes governed by stochastic Langevin dynamics with a colored random force, corresponding to a noise generated by an Ornstein−Uhlenbeck process. Such non-Markovian dynamics take place in a variety of chemical and biological systems. Using the path integral approach, we constructed the conditional probability for passing between two stationary states in configurational space. Our relations can be used for Monte Carlo sampling of evolution trajectories for systems with many degrees of freedom as well as for determining the reaction coordinate used in transition state theory. On the basis of our relation for a conditional probability, we generalize the method of determining the most probable path to the case of colored random force. Using the simple three-hole potential, we examine numerically the effect of nonzero correlation time (memory) on the evolution of the most probable path for a finite temperature.

I. Introduction

Although the methodology of chemical reactions in the gas phase is rather well developed, similar processes in condensed phases are still under earlier stages of investigation.[1] There are several proposed approaches to the description of various activation processes in such complex systems. However, there is still no single approach applicable to every kind of reaction. One of the main restrictions comes from our numerical abilities. Some molecular processes in chemistry and biology occur on time scales that range from femtoseconds to minutes and more. There have been several attempts to develop the methodology that enables studies of biochemical phenomena not accessible to molecular dynamics simulations.[2−5]

Another reason for computational difficulties comes from the fact that most transitions are rare events. Conventional methods for studying rare events in condensed phases are based on transition state theory.[6−9] When a typical activation process occurs, many degrees of freedom will generally contribute to transport the system from one stable region to another, crossing a dynamical bottleneck called a transition state. The latter is usually defined as the saddle point that the system has to pass in order for the reaction to occur.[10−12] Indeed, while determining minima of potential energy surfaces is relatively easy, locating transition states, which are first-order maxima on the potential energy surface, is much more difficult. Furthermore, in some cases it is desirable to locate all the transition states connecting two given minima. If that is possible, then the intrinsic reaction coordinate can be chosen to establish connecting minima.

Probably the most popular approach to treat rare events in recent years is associated with the path sampling method developed by Chandler and coauthors.[13−19] However, one of the crucial features of this method is its Markovian nature. At the same time, all the processes in nature are non-Markovian to some degree. We never can say in advance what the time correlation is for arbitrary systems. Although the importance of memory effects is well realized in some specific problems, for example surface diffusion,[20−22] there is still no general approach to account for time-correlations in chemical reactions.

Perhaps the most successful theory to embrace the memory effects in activation processes has been developed by Grote and Hynes[23,24] and their successors. They generalized the original Kramers theory[25] to include non-Markovian effects in the evolution of the reaction coordinate. More recent developments of the Grote−Hynes theory can be found in refs 26−28 and the references therein. Despite the obvious success in the number of practical problems, the Grote−Hynes theory still has the same restriction as the original Kramers theory. It deals with the dynamics of the ideal reaction coordinate assuming a very high activation barrier. In many practical problems, it is extremely difficult to locate all the transition states involved in the reaction, which produces technical limitations to the usefulness of this approach.

The main goal of the present paper is to propose an alternative description of rare events with account of their non-Markovian nature. For this purpose, we use the path integral technique in its probabilistic sense. As an example, we calculate the most probable path for the system at finite temperature, which is important for various techniques. Particularly, it can help in determination of the reaction coordinate in transition state theory[6−9] or in finding the initial successful path in the stochastic path sampling method.[13−19]

The paper is constructed as follows. In Section II we present the general formalism of probability path integral construction. Starting with a set of Langevin-like equations with exponentially correlated random forces, we evaluate the path probability density in the configurational space of the system. This allows us to construct in Section III the conditional probability for the

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system to pass through the activation barrier. A knowledge of this *success* probability for reaction to occur gives the straightforward algorithm for computing the reaction rate. On the other hand, the path integral representation is very convenient for calculation of the most probable path (MPP), which is a natural reaction coordinate in many chemical processes. Using the variational principle, we derive a differential equation for MPP. As an general example, in Section IV we examine the influence of nonzero correlation time to the temperature dependence of the reaction coordinate. A numerical example of the memory effect in the temperature dependence of MPP is given in Section V. Finally, we outline our results in Section VI.

II. General Formalism

Let us consider a system which, though not in equilibrium, can still be characterized by a finite complete set of variables q_i ($i = 1...n$), whose evolution is governed by the matrix Langevin equation

$$M\ddot{Q} = -\Gamma(t)\dot{Q} - \frac{\mathrm{d}}{\mathrm{d}Q}U(Q) + F(t) \tag{1}$$

where $Q = (q_1,..., q_n)^T$, $\Gamma(t)$, M, and $F(t)$ are the diagonal matrices, consisting of the time-dependent damping coefficients, masses, and random forces, respectively. The microscopic origin of the Langevin equation as well as the approximations involved are discussed in Appendix A.

When the force $F(t)$ in eq 1 is delta correlated, i.e., $\langle F(t_i)F(t_j)\rangle = 2D\delta(t_i - t_j)$, the solution process $Q(t)$ is a Markov process. However, in real chemical systems the forces encountered have nonzero correlation time. For the purpose of generality, we consider here the non-Markovian case, which is much closer to reality. However, to simplify the picture, we suppose the force $F(t)$ to be Gaussian. For this case we have[29]

$$\langle F(t)\rangle = 0$$
$$\langle F(t_i)F(t_j)\rangle = \frac{D}{\tau}\exp\left(-\frac{|t_i - t_j|}{\tau}\right) \tag{2}$$

where D is the random force strength, τ is the correlation time, and the angular brackets represent an ensemble average. We have chosen the specific form of force−force correlation in eq 2 that corresponds to noise generated by an Ornstein−Uhlenbeck process,[29] widely used in various stochastic problems. In what follows, we restrict ourselves with this particular coloration.

We have to emphasize here that our set of equations (eq 1) has rather different meaning from what is exploited in, say, Kramers or Grote−Hynes theories. The Kramers approach and all its modifications deal with the Langevin equation along the *ideal* reaction coordinate, which is supposed to be known from the beginning. On the contrary, our set (eq 1) incorporates all the slow variables in the system. In fact, it can contain both relevant and irrelevant variables for a chemical process under study. This means that we do not restrict ourselves to an ideal reaction coordinate, which generally cannot be always known in advance. It is of special importance for complex systems with many possible transition states and/or low activation barriers.

Using the fact that $F(t)$ (and therefore D) is a square diagonal matrix, it can be rigorously shown (see Appendix B for details) that the path *probability density* $\mathscr{P}\{F(t)\}$ over the interval (0,t) is given by

$$\mathscr{P}\{F(t)\} \propto \exp\left\{-\frac{1}{4D}\int_0^t \mathrm{d}s[F^2(s) + \tau^2\dot{F}^2(s)]\right\} \tag{3}$$

We note that, until now, we did not use any particular discretization of the initial equations of motion (eq 1). However, we need to use a representation in discrete time steps to pass from a random force to coordinate description. According to the understanding of the functional integral in the probabilistic sense, the quantity $\mathscr{P}\{F(t)\}\mathscr{D}F(t)$ is the probability for paths, i.e., an expression for the number of realizations of the stochastic process lying in the region $F(t)$ to $F(t) + \mathscr{D}F(t)$. Now, using the equality

$$\int \mathscr{D}F(t)\mathscr{P}\{F(t)\} = \int \mathscr{D}Q(t)\mathscr{P}\{Q(t)\} \tag{4}$$

we can write the corresponding probability in coordinate representation as

$$\mathscr{D}Q(t)\mathscr{P}\{Q(t)\} \propto \mathscr{D}Q(t)J[Q(t)]\exp\left(-\frac{S[Q(t)]}{4D}\right) \tag{5}$$

where the effective action is given by

$$S[Q(t)] = \sum_0^t \mathrm{d}t\left\{\left[M\ddot{Q} + \Gamma\dot{Q} + \frac{\mathrm{d}}{\mathrm{d}Q}U(Q)\right]^2 + \tau^2\left[M\ddot{Q} + \Gamma\ddot{Q} + \dot{Q}\frac{\mathrm{d}^2}{\mathrm{d}Q^2}U(Q)\right]^2\right\} \tag{6}$$

and

$$J[Q(t)] = \frac{\mathscr{D}F(t)}{\mathscr{D}Q(t)} \tag{7}$$

is the Jacobian of transformation from the $F(t)$ realization to the $Q(t)$ realization over the same time interval. The details of the calculations of the Jacobian are presented in Appendix C. The main outcome is the Jacobian (eq 7) does not depend on the system's coordinates. Also it is shown that including the inertial term, i.e., the acceleration $\ddot{Q}$, leads to a unique result for different types of discretization.

III. Sampling Evolution Trajectories and the Reaction Coordinate

Let us discuss the practical importance of the obtained relations 5−7. Any average of an arbitrary functional defined on a fixed time interval can, in principle, be evaluated via the path integral of this functional with the weight

$$J[Q(t)]\exp\left(-\frac{S[Q(t)]}{4D}\right) \tag{8}$$

where $S[Q(t)]$ is given by eq 6. The implementation of such a procedure in practice can be done following the scheme of Chandler's group.[13−19] Although the latter approach was initially constructed to be essentially Markovian, the memory is already accounted for in our weight function.[8]

Furthermore, the proposed treatment gives us even more advantage. If we consider some stochastic process described by a set of trajectories that start at the *reactant* coordinate Q_r and end at the *product* coordinate Q_p, then the corresponding conditional probability is given by

$$\mathbb{P}(Q_r|Q_p, t) \propto \int \mathscr{D}Q(t)\exp\left\{-\frac{1}{4D}\int_0^t \mathrm{d}t\left(\left[M\ddot{Q} + \Gamma\dot{Q} + \frac{\mathrm{d}}{\mathrm{d}Q}U(Q)\right]^2 + \tau^2\left[MQ + \Gamma\ddot{Q} + \dot{Q}\frac{\mathrm{d}^2}{\mathrm{d}Q^2}U(Q)\right]^2\right)\right\} \tag{9}$$

where functional integration is performed over all possible path realizations between reactant and product states.

In practical problems, it is sometimes useful to rewrite eq 9 in a discrete form as

$$\mathbb{P}(Q_\mathrm{r}|Q_\mathrm{p}, t) \propto \int_{Q_1}\cdots\int_{Q_N}\prod_{i=1}^{N}\mathrm{d}Q_i \exp\Bigg\{-\frac{\Delta t}{4D}\sum_{j=1}^{N+1}\Bigg(\Bigg[\frac{M}{(\Delta t)^2}(Q_j - 2Q_{j-1} + Q_{j-2}) + \frac{\Gamma}{2\Delta t}(Q_j - Q_{j-2}) + \frac{\mathrm{d}}{\mathrm{d}Q_{j-1}}U(Q_{j-1})\Bigg]^2 + \tau^2\Bigg[\frac{M}{(\Delta t)^3}(Q_j - 3Q_{j-1} + 3Q_{j-2} - Q_{j-3}) + \frac{\Gamma}{(\Delta t)^2}(Q_j - 2Q_{j-1} + Q_{j-2}) + \frac{1}{2\Delta t}(Q_j - Q_{j-2})\frac{\mathrm{d}^2U}{\mathrm{d}Q_{j-1}{}^2}\Bigg]^2\Bigg)\Bigg\} \tag{10}$$

where we have identified Q_0 and Q_{N+1} with the reactant and product coordinates, respectively. The obtained discrete matrix expression (eq 10) is one of the main results of this paper. It can be used for Monte Carlo sampling of paths following, say, the Pratt scheme,[30] when the process under consideration is non-Markovian. It is also useful for direct estimation of transition rates in colored systems, following the approach of Chandler's group[9,13−19] or using the adaptive importance sampling technique.[31,32]

In practice, we must decide for every given system which approach is more appropriate, i.e., the path sampling method with the weight functional (eq 8) or the direct evaluation of the rate. The latter seems to be easier to implement for systems with a high activation barrier, while the former is more general.

Another advantage of the results of eqs 9 and 10 is that they allow us to calculate the most probable path of reaction, which generally can be used as the natural reaction coordinate in simulations of chemical processes. Indeed, the limit $D \to 0$, $\mathbb{P}(Q_\mathrm{r}|Q_\mathrm{p}, t)$ given in eq 9 reaches a maximum when the action $S[Q(t)]$ is minimal. Thus, the major contribution to the path integral arises around a path that minimizes the action $S[Q(t)]$ in reaching Q_p from Q_r. The mathematical condition for minimizing the action is

$$\frac{\delta S[Q(t)]}{\delta Q(t)} = 0 \tag{11}$$

Condition 11 can be exploited relatively easily analytically. To proceed, let us rewrite eq 6 as

$$S[Q(t)] = \int \mathrm{d}Q\,\mathscr{L}(\dddot{Q}, \ddot{Q}, \dot{Q}, Q; t) \tag{12}$$

where $S[Q(t)]$ and $\mathscr{L}(\dddot{Q}, \ddot{Q}, \dot{Q}, Q; t)$ stand for the analogs of the action and Lagrangian of some non-mechanical dynamical system. It can be rigorously proved that if the initial and final positions are fixed and stationary, then condition 11 leads to the analog of the Euler−Lagrange equation for the formulated optimization problem:

$$\frac{\partial\mathscr{L}}{\partial Q} - \frac{\mathrm{d}}{\mathrm{d}t}\frac{\partial\mathscr{L}}{\partial\dot{Q}} + \frac{\mathrm{d}^2}{\mathrm{d}t^2}\frac{\partial\mathscr{L}}{\partial\ddot{Q}} - \frac{\mathrm{d}^3}{\mathrm{d}t^3}\frac{\partial\mathscr{L}}{\partial\dddot{Q}} = 0 \tag{13}$$

At this point we have to note that $S[Q(t)]$ and $\mathscr{L}(\dddot{Q}, \ddot{Q}, \dot{Q}, Q; t)$ are not related to the corresponding physical quantities in mechanical systems. We use these notations to make the mathematical analogy clear.

Direct implementation of eq 13 to the Lagrangian yields a sixth-order nonlinear differential equation for $Q(t)$:

$$\tau^{-2}\{U'U'' + (2MU'' - \Gamma^2)\ddot{Q} + M\dot{Q}^2U''' + M^2Q^{(4)}\} = U''(2MQ^{(4)} + \ddot{Q}U'' + \dot{Q}^2U''') - \Gamma(\Gamma Q^{(4)} + 3\dot{Q}\ddot{Q}U''' + \dot{Q}^3U'''') + M(Q^{(6)} + 4\dot{Q}\dddot{Q}U''' + 3\ddot{Q}^2U''' + 6\dot{Q}^2\ddot{Q}U'''' + \dot{Q}^4U''''') \tag{14}$$

where dashes represent derivatives with respect to Q, and $Q^{(n)}$ means the *n*th derivative with respect to time whenever it is higher than the third one. For a limiting test of eq 14, we can ignore the memory contribution ($\tau = 0$) and set $\Gamma = 0$ to obtain

$$U''(U' + 2M\ddot{Q}) + M(MQ^{(4)} + \dot{Q}^2U''') = 0$$

which is rigorously satisfied when the system's evolution obeys classical Newtonian equations of motion, $U' + M\ddot{Q} = 0$.

Equation 14 gives us a precise way to determine the most probable trajectory of the system. To our knowledge, it is the only way to define the reaction coordinate for an arbitrary system. Furthermore, knowing the solution for eq 14 allows one to construct the corresponding Fokker−Planck equation (see Appendix D). However, we have to solve it with suitable boundary conditions, which is not a simple task. Alternatively, we could try to find an approximate successful reaction coordinate that is not too far from the solution of eq 14. One possibility to do this was recently proposed by Elber and Shalloway[33] for the simple overdamped Brownian system subjected to a white random force.

IV. Temperature-Dependent Reaction Coordinate

In general, the particular way to calculate the MPP depends on the features of a specific system. However, we still can examine some interesting general consequences of nonzero time correlation. Specifically, here we investigate the influence of memory on the temperature dependence of the MPP (or reaction coordinate, if we identify it). In order to obtain the exact MPP, we still need to solve the differential eq 14. However, an analysis of the temperature behavior of MPP can be done relatively easily when τ is small enough to neglect the time dependence of the damping matrix Γ in eq 1. This is a good approximation for high activation barriers and small or moderate temperatures. By doing a series of routine integration by parts, we can rewrite the effective action as follows (see Appendix E):

$$S[Q(t)] = S_\mathrm{cl}[Q(t)] + \tilde{S}[Q(t)] \tag{15}$$

where $S_\mathrm{cl}[Q(t)]$ stands for the *classical* part of the action

$$S_\mathrm{cl}[Q(t)] = \int_0^t \mathrm{d}t\left\{\left(M\ddot{Q} + \Gamma\dot{Q} + \tau\dot{Q}\frac{\mathrm{d}^2}{\mathrm{d}Q^2}U(Q)\right)^2 + \left(\frac{\mathrm{d}}{\mathrm{d}Q}U(Q)\right)^2\right\} \tag{16}$$

and

$$\tilde{S}[Q(t)] = 2\tau\Gamma\int_0^t \mathrm{d}t(\ddot{Q} - \tau\dddot{Q})U' + 2\tau M\int_0^t \mathrm{d}t(\dddot{Q} - \tau\ddddot{Q})U' \tag{17}$$

In order to obtain the MPP, we have to minimize both parts of the functional.[15] Here the structure of $\tilde{S}[Q(t)]$ helps us to simplify the problem. Indeed, this part of the action must be nonnegative to ensure path stability; then the minimal value of $\tilde{S}[Q(t)]$ must be zero. This can also be shown applying the variational procedure, similar to what was done at the end of

Section III. So our further aim is to minimize only the classical part of the action.[16] The latter can be represented as

$$S_{\mathrm{cl}}[Q(t)] = \int_0^t \mathrm{d}t \left\{ \frac{\mathscr{M} \dot{X}_\tau^{\,2}}{2} - V(X_\tau) \right\} \tag{18}$$

where we have introduced the new coordinate vector

$$X_\tau = Q\left(1 + \frac{\tau}{\Gamma} \frac{\mathrm{d}^2}{\mathrm{d}Q^2} U(Q)\right) + \frac{M}{\Gamma} \dot{Q} \tag{19}$$

and made a formal replacement $\mathscr{M} = 2\Gamma^2$ and $V(X_\tau) = -(\mathrm{d}/\mathrm{d}Q\ U(Q))^2$.

Further analysis is rather similar to what is done in ref 33. We, however, briefly reproduce it here in order that this study be self-consistent. Let us define the alternative classical Lagrangian

$$\mathscr{L}_{\mathrm{cl}} = \Gamma^2 \dot{X}_\tau^{\,2} + \left(\frac{\mathrm{d}}{\mathrm{d}Q} U(Q)\right)^2 \tag{20}$$

By defining the corresponding classical momentum,

$$p = \frac{\partial \mathscr{L}}{\partial \dot{X}_\tau} = 2\Gamma^2 \dot{X}_\tau \tag{21}$$

as well as the classical Hamiltonian, $\mathscr{H}_{\mathrm{cl}} = p\dot{X}_\tau - \mathscr{L}_{\mathrm{cl}}$, we can rewrite the classical action in the following standard form:

$$S_{\mathrm{cl}} = \int_{0t} (p\dot{X}_\tau - \mathscr{H}_{\mathrm{cl}})\mathrm{d}t = \int_{X_\tau(0)}^{X_\tau(t)} p\,dl - \int_{0t} \mathscr{H}_{\mathrm{cl}}\mathrm{d}t \tag{22}$$

Following ref 33, we consider the total time t as an input. In this case, there is a constant Hamiltonian $\mathscr{H}_{\mathrm{cl}}^{(\mathrm{s})}$, which preserves the stationary path. Mathematically, it is expressed as

$$\frac{\delta S_{\mathrm{cl}}}{\delta l} = 0$$

$$S_{\mathrm{cl}} = \int_{X_\tau^{(\mathrm{r})} X_\tau^{(\mathrm{p})}} p\,dl_{\mathrm{s}} - \int_{0t} \mathscr{H}_{\mathrm{cl}}^{(\mathrm{s})}\mathrm{d}t = \int_{X_\tau^{(\mathrm{r})} X_\tau^{(\mathrm{p})}} p\,dl_{\mathrm{s}} - \mathscr{H}_{\mathrm{cl}}^{(\mathrm{s})} t \tag{23}$$

Since the last term in eq 23 is path independent, the variation of S_{cl} is equivalent to the variation of the subaction $\tilde{S}_{\mathrm{cl}} = \int_{X_{\mathrm{t}}^{(\mathrm{r})}}^{X_{\mathrm{t}}^{(\mathrm{p})}} p\,dl_{\mathrm{s}}$. Using the standard classical mechanics formula $p = \sqrt{2\mathscr{M}(E - V(X_\tau))}$, the subaction can be represented as

$$\tilde{S}_{\mathrm{cl}} = 2\Gamma \int_{X_\tau^{(\mathrm{r})}}^{X_\tau^{(\mathrm{p})}} dl \sqrt{\mathscr{H}_{\mathrm{cl}}^{(\mathrm{s})} + \left(\frac{\mathrm{d}}{\mathrm{d}Q} U(Q)\right)^2} \tag{24}$$

The only yet undetermined quantity in our consideration is $\mathscr{H}_{\mathrm{cl}}^{(\mathrm{s})}$. To find this, we assume that the reactant state of the system corresponds to its thermal equilibrium, so that, at $t = 0$, $\mathscr{H}_{\mathrm{cl}}^{(\mathrm{s})}$ can be expressed as

$$\mathscr{H}_{\mathrm{cl}}^{(\mathrm{s})} = \frac{p^2(0)}{2\mathscr{M}} - \left(\frac{\mathrm{d}}{\mathrm{d}Q} U(Q_{\mathrm{r}})\right)^2 = \frac{p^2(0)}{4\Gamma^2} \approx \frac{nk_{\mathrm{B}}T\Gamma^2}{m} \tag{25}$$

where n is the number of degrees of freedom, k_{B} is the Boltzmann constant, and T is the characteristic temperature. Thus, using the simple analogy with classical mechanics of a point-like particle in one dimension, we show that the reaction coordinate can be chosen as a stationary path l_{s}, that minimizes the functional

$$\mathcal{S} = \int_{Q_{\mathrm{r}}}^{Q_{\mathrm{p}}} \mathrm{d}l \left\{ \frac{nk_{\mathrm{B}}T\Gamma^2}{m} \left(1 + \frac{\tau}{\Gamma} \frac{\mathrm{d}^2}{\mathrm{d}Q^2} U(Q)\right) + \left(\frac{\mathrm{d}}{\mathrm{d}Q} U(Q)\right)^2 \right\}^{1/2} \tag{26}$$

The corresponding time is thus given by

$$t = \Gamma \int_{Q_{\mathrm{r}}}^{Q_{\mathrm{p}}} \mathrm{d}l \left\{ \frac{nk_{\mathrm{B}}T\Gamma^2}{m} \left(1 + \frac{\tau}{\Gamma} \frac{\mathrm{d}^2}{\mathrm{d}Q^2} U(Q)\right) + \left(\frac{\mathrm{d}}{\mathrm{d}Q} U(Q)\right)^2 \right\}^{-1/2} \tag{27}$$

Note that, if we set the correlation time to be zero, $\tau = 0$, then the result (eq 28) coincides with the corresponding functional obtained in ref 33 for the system subjected to a white force. Expression 28 works for both systems with or without the inertial term (acceleration) of the Langevin equation. However, the account of the inertial term allows us to unify the result independently of the discretization used.

We see that the account of the memory effect changes the result through the second derivative of the potential. We can introduce an effective temperature,

$$T^* = T\left(1 + \frac{\tau}{\Gamma} \frac{\mathrm{d}^2}{\mathrm{d}Q^2} U(Q)\right) \tag{28}$$

to reduce formulas 27 and 28 to look formally as the case of a white force. However, the memory effect does affect even the limiting cases. In the case of zero temperature, we have

$$\mathcal{S} = \sum_{Q_{\mathrm{r}}}^{Q_{\mathrm{p}}} \mathrm{d}l \left| \frac{\mathrm{d}}{\mathrm{d}Q} U(Q) \right| \tag{29}$$

which corresponds to the steepest descent path. However, another limiting case of high temperatures gives

$$\mathcal{S} = \Gamma \sqrt{\frac{nk_{\mathrm{B}}T}{m}} \int_{Q_{\mathrm{r}}}^{Q_{\mathrm{p}}} \sum_{Q_{\mathrm{r}}}^{Q_{\mathrm{p}}} \mathrm{d}l \left(1 + \frac{\tau}{\Gamma} \frac{\mathrm{d}^2}{\mathrm{d}Q^2} U(Q)\right)^{1/2} \tag{30}$$

which is not simply a straight line as in the case of white forces. It becomes a straight line only for small τ or very strong damping. However, we should be very careful with certain physical conclusions here, because our initial construction of the Langevin equation assumes only moderate temperatures. Otherwise, we have to account for the time dependence of the memory function in eq 1. An even more important restriction for the temperature comes from the approximation done when obtaining eq 26. Following the authors of ref 33, we require the particle to be thermalized at $t = 0$, but start to move *exactly* from the minimum point, where $\mathrm{d}U/\mathrm{d}Q = 0$. Of course, this approximation is not good for high temperatures. Nevertheless, we can examine the memory effect on the system dynamics under appropriate conditions. This is done in the next section with the simple Huo–Straub potential.[34]

V. Numerical Illustration

We consider the optimal paths in the 2D ($n = 2$) potential with three minima, Figure 1, considered in refs 33 and 34:

$$U(x, y) = -5\mathrm{e}^{-y^2}[\mathrm{e}^{-(x-1)^2} + \mathrm{e}^{-(x+1)^2}] - 3\mathrm{e}^{-x^2}[\mathrm{e}^{-(y-5/3)^2} - \mathrm{e}^{-(y-1/3)^2}] \tag{31}$$

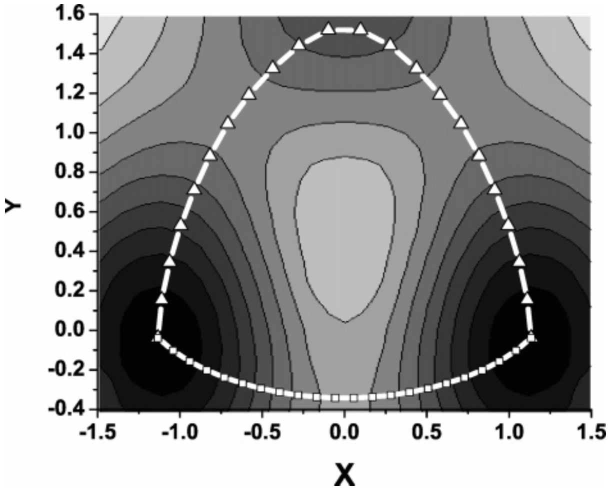

Figure 1. The “longer” (triangles) and “shorter” (squares) optimal paths for the three-minima potential, eq 31. The potential is shown as a contour plot.

We discretize the action $\mathcal{S}$, eq 26, in space in the following way:[35]

$$2\mathcal{S}_{\text{discrete}} = \Delta l_{0,1} I_0 + \Delta l_{N,N+1} I_{N+1} + \sum_{i=1}^{N} (\Delta l_{i-1,i} + \Delta l_{i,i+1}) I_i + \lambda \sum_{i=0}^{N} (\Delta l_{i,i+1} - \langle \Delta l \rangle)^2 \quad (32)$$

$$\Delta l_{i,i+1} = \sqrt{(Q_i - Q_{i+1})^2}$$

$$I_i = \left\{ \frac{2k_B T \Gamma^2}{M} \left(1 + \frac{\tau}{\Gamma} \frac{d^2}{dQ_i^2} U(Q_i) \right) + \left(\frac{d}{dQ_i} U(Q_i) \right)^2 \right\}^{1/2}$$

$$\langle \Delta l \rangle = \frac{1}{N} \sum_{i=0}^{N} \Delta l_{i,i+1} \quad (33)$$

The discretization is done on a grid of $N = 20$ space points $Q_i \equiv (x_i, y_i)$, $i = 1...N$, plus the initial (0th) and final [$(N + 1)$th] points, chosen to correspond to the two lowest minima of the potential. The term proportional to λ in the action $\mathcal{S}_{\text{discrete}}$ causes different discretization intervals along the path to have equal lengths, and it does not affect the value of the action if this condition is satisfied exactly. The value of $\lambda = 100$ is used throughout.

The paths are optimized using the “downhill simplex” technique.[36] The optimization runs are stopped at points where the relative changes of the action $\mathcal{S}_{\text{discrete}}$ do not exceed 10^{-10}, and they are restarted several times to ensure the final convergence. Besides, in the separate control runs with two generalizations of the above technique, involving simulated annealing[36] and subspace searching,[37] we check that the results do not depend on the optimization details. The optimization techniques used, though slower than the methods where the knowledge of the gradient of the function being optimized is required, have a clear advantage in that they permit a study of the cases where the action depends on the coordinates in a very complicated manner.

As illustrated in Figure 1, there are two different optimal paths joining the two lowest minima of the potential: the “longer” path going through the third, “intermediate” minimum, and the “shorter” direct one. For lower intervals of temperature, both paths are stable; however, as the temperature is increased, the “longer” path sharply disappears at some temperature. In the absence of memory effects ($\tau = 0$), the transition temperature is numerically found to correspond to $H_0 = nk_B T_0 \Gamma^2/M \approx 1.3040 \pm 0.0002$ (the temperature is expressed through an “effective Hamiltonian” $H = nk_B T \Gamma^2/M$, that appears in the expression for the action eq 26).

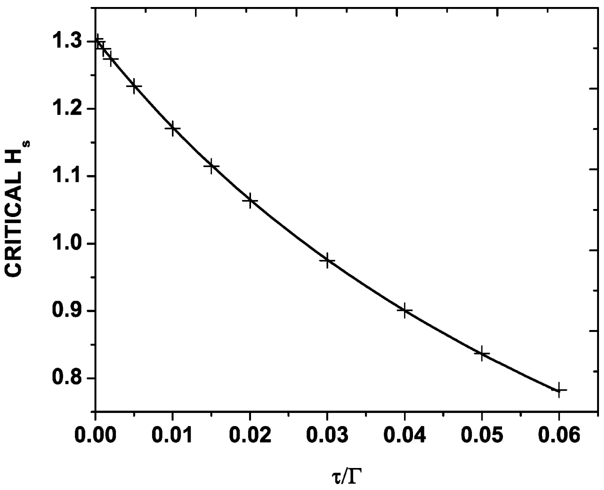

Figure 2. Value of the normalized temperature $H = nk_B T \Gamma^2/M$ for the transition from the “longer” to the “shorter” path as a function of the correlation time τ/Γ.

We now inquire as to how the memory effect changes the temperature at which the “longer” path disappears. Numerically we determine that this transition temperature decreases with τ, and this decrease can be very precisely fitted by a simple curve,

$$H = \frac{H_0}{1 + \beta \tau/\Gamma} \quad (34)$$

with the constant coefficient $\beta = 11.20 \pm 0.02$ (see Figure 2). This functional form can be explained simply in terms of the effective temperature introduced by eq 28. Indeed, according to eq 28, the presence of the nonzero memory term effectively modifies the temperature of the system approximately as $T^* = T(1 + \tau/\Gamma \cdot d^2U/dQ^2)$, where d^2U/dQ^2 is just the Laplacian of the potential $U(Q)$ along the path. Namely, the memory effects lead to the local “heating” of the system in those parts of the path where the Laplacian of the potential is positive ($d^2U/dQ^2 > 0$), i.e., near the minima, and on the other hand, the system is locally “cooled down” in the parts of the path where the Laplacian is negative, i.e., near the maxima of the reaction potential.

In the case of a system with memory ($\tau > 0$), it is this local effective temperature T^* (rather than the Langevin temperature T itself) that defines the criterion for the stability/instability of a given path at a given T. (This also strongly affects the transition rate, because it is now dependent on the new effective temperature T^*.) For example, when T is increased, the instability of the “longer” path (Figure 1) starts from its middle part. It is this middle part that passes near/through the third, local minimum of the reaction potential, where the Laplacian is found to be a large positive value of $d^2U/dQ^2 \approx 10$. This should lead to local heating of the system, according to eq 28.

Thus, for a system with memory, in order to determine the transition temperature for the disappearance of the “longer” path, it is the increased local effective temperature of the middle part of the path $T^*_{\text{middle}} = T(1 + \tau/\Gamma \cdot (d^2U/dQ^2)_{\text{middle}})$ that should be equated to the “critical” value $T_0 = H_0 M/nk_B \Gamma^2$, as measured for the case of zero memory, $\tau = 0$. Hence, one obtains eq 34 with the coefficient $\beta \approx (d^2U/dQ^2)_{\text{middle}}$ identified as the value of the Laplacian of the potential in the middle part of the path. The numerical coincidence of the values for $\beta \approx 11.20$ as determined from fitting versus $(d^2U/dQ^2)_{\text{middle}} \approx 10$, as determined directly from the path, is quite satisfactory. Let us note here, that the local heating of the system near the initial and final points of the optimal path, i.e., near the two main minima where the Laplacian is also large positive, does not seem to play any role in the stability of the path, possibly because these regions lie far from the most "sensitive" middle part of the path.

In summary, the explanation of the stability of the path in terms of the effective local "heating/cooling" of the system due to memory effects seems reasonable, and, to the best of our knowledge, this idea is also new. It would be interesting to further confirm the validity of this idea with more realistic models.

VI. Conclusions

The focus of our study is a chemical system which obeys Langevin dynamics (eq 1) with colored random force (eq 2). Using the path integral technique, we construct conditional probability 9 for the system to pass successfully from the reactant state to the product. Our formulas 9 and 10 do not depend on the particular discretization of the equations of motion and can be directly used for either the path sampling of non-Markovian systems or direct evaluation of the reaction rates. Using variational principle 11, we give the differential eq 14 for the most probable path (MPP) of reaction. However, in view of its complexity, we use our general relations 9 and 10 to generalize recent calculations[33] of the most probable path to the case when the inertial term is accounted for in the Langevin equation. By considering nonzero correlation time, we examine how important the memory effect is for MPP calculations, and we demonstrate our results numerically with a three-hole potential model (eq 31).

Finally, we would note that our approach in principle can be applied to any activation process, although would be mostly used for processes where the memory effects are essential. In addition to the surface diffusion problem,[20−22] chemically important examples of such processes include S_N2 -like reactions in water, which have been shown to involve considerable non-Markovian effects.[38,39] These kind of reactions are of special importance for studies of heavy-particle charge-transfer reactions in solution.[40−42] Another expected important application of the proposed framework is the interconversion process between an ion pair and solvent.[43] These types of processes play an important role in a wide range of chemical and biological problems, like macromolecular catalysis,[44] biochemical hydrolysis mechanisms,[45] and protein stability.[46,47]

Our approach also allows the investigation of noise-induced rate processes between macroscopic systems states subject to external noise, which experiments already are able to do quite precisely.[48] Another notable advantage of the developed framework is an account of the inertial term in the Langevin equation, which is important in situations where the evolution is not overdamped. This should be useful in the analysis of fast processes, such as low-barrier isomerization dynamics.[49,50]

Of course, the above examples do not exhaust all the problems manifesting strong memory effects. The practical implementation of the proposed approach will be the goal of our future studies.

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Appendix A: Langevin Dynamics

Accurate numerical investigations of chemical reactions and, more generally, activation processes can be done by different techniques. Probably the most straightforward one is a microscopically detailed molecular dynamics simulation. However, for real systems it is often too time extensive and expensive. Moreover, such detailed simulations sometimes take into account degrees of freedom which are not important for the outcome but require a lot of resources to simulate them. For these cases, there are various theoretical techniques developed to reduce unimportant degrees of freedom, or, roughly speaking, to integrate equations of motion over them.

The Langevin equation (and equivalently the Fokker−Planck equation) is often used in a phenomenological approach, with the choice of a model adiabatic potential and a friction parameter. However, it could be derived rigorously from microscopic Hamiltonian equations that incorporate all the degrees of freedom in the system. Probably, the most comprehensive approach to this problem can be done by the use of Mori projection operator techniques.[20,21,51−54] The basic idea is to separate the variables into two Hilbert subspaces, one for the *slow* degrees of freedom denoted here by Q to be treated explicitly, and one for the *fast* degrees of freedom to be integrated out. The particular choice of these subspaces depends on the nature of the system under consideration. Ideally, the procedure of degrees reduction must be done for each system under study individually. When we identify the corresponding subspaces, we can define a projection operator $\mathcal{P}$ onto the subspace of slow variables and the orthogonal projection operator $\mathcal{Q} = 1 - \mathcal{P}$. By projecting out all the fast degrees of freedom, we end up with a generalized Langevin equation of motion of the form

$$M\ddot{Q}(t) = -\int_{-\infty}^{t} \Sigma\,(t, t')\dot{Q}(t')\mathrm{d}t' - \frac{\mathrm{d}}{\mathrm{d}Q}U(Q) + F(t) \tag{A-1}$$

where M is the effective mass, $U(Q)$ is the adiabatic potential, and $F(t)$ is the random force. The damping of slow degrees is characterized by a memory function $\Sigma(t,t')$ that usually depends in a complicated manner on the past history of the system evolution. Importantly, the memory function $\Sigma(t,t')$ and the fluctuating force $F(t)$ in eq A-1 are not independent of each other since they both arise from the coupling to the fast variables subspace. These quantities are related by the fluctuation−dissipation theorem[55]

$$\Sigma\,(t_i,t_j) = \frac{1}{k_B T}\langle F(t_i)F(t_j)\rangle \tag{A-2}$$

The random force $F(t)$ is the component of the total force projected out of the subspace of slow degrees and generally has a very complicated time dependence given by

$$F(t) = -\exp\{-i\,\mathcal{Q}\mathcal{L}\mathcal{Q}\,t\}\,\frac{\mathrm{d}}{\mathrm{d}Q}U(Q) \tag{A-3}$$

where $\mathcal{L}$ is the Liouville operator. Usually the correlator in eq A-2 is approximated in some manner. The simplest form of memory function occurs in the Markovian limit, where the time scale for the fast degrees of freedom is set to be zero. In this case, the memory function is approximated by a delta function, and the first term on the right-hand side (RHS) of eq A-1 becomes $\Gamma\dot{Q}$, where Γ is a constant. This is a common approximation in treatments of chemical reactions. Less severe approximations can be done in the manner similar to the Grote–Hynes theory[23,24] to account for memory effects. In this case, the first term on the RHS of eq A-1 is approximated as $\Gamma(t)\text{-}\dot{Q}(t)$, where $\Gamma(t)$ is the matrix of time-dependent damping coefficients.

Appendix B: Probability Density Function

All the matrices involved in the Langevin eq 1 are assumed diagonal, which allows us to work with them similarly to one-dimensional equations. We assume the random force $F(t)$ to be Gaussian with zero mean. Since the process is defined over an infinite time interval, it is convenient to work with the Fourier transform of the correlator defined in eq 2,

$$\langle F(\omega)F(\omega')\rangle = 2\pi DK(\omega\tau)\delta(\omega-\omega') \tag{B-1}$$

where

$$K(\omega\tau) = \int_0^\infty \mathrm{d}sK(s)\exp(i\omega\tau s) + \text{c.c.} = \frac{2}{1+\omega^2\tau^2} \tag{B-2}$$

If the probability density functional is Gaussian, then using $\langle F(\omega)\rangle = 0$ and eq B-1, we can write[56]

$$\begin{aligned}\mathscr{P}\{F(t)\} &\propto \exp\left\{-\frac{1}{2D}\int_{-\infty\infty}\frac{\mathrm{d}\omega}{2\pi}F(-\omega)K^{-1}(\omega\tau)F(\omega)\right\}\\ &= \exp\left\{-\frac{1}{4D}\int_{-\infty}^{\infty}\frac{d\omega}{2\pi}F(-\omega)(1+\omega^2\tau^2)F(\omega)\right\}\\ &= \exp\left\{-\frac{1}{4D}\int_{-\infty}^{\infty}dtF(t)(F(t)-\tau^2\ddot{F}(t))\right\}\\ &= \exp\left\{-\frac{1}{4D}\int_{-\infty}^{\infty}\mathrm{d}t(F^2(t)+\tau^2\dot{F}^2(t))\right\}\end{aligned} \tag{B-3}$$

which is consistent with eq 3 in the main text.

Appendix C: Calculation of the Jacobian, Eq 7

In calculating the Jacobian in eq 7, we have to resort to a limiting process that starts with a representation in discrete time steps. Specifically, we may choose

$$\Delta t = t/N = t_j - t_{j-1};\ j = 1,\ldots, M;\ t_0 = 0 \tag{C-1}$$

Further, we can put $Q_j = Q(t_j)$ and

$$F_j = \int_{t_{j-1}}^{t_j}\mathrm{d}sF(s) \tag{C-2}$$

Carrying through this procedure in detail, we arrive at a recursive relation of the form

$$F_j = \frac{M}{\Delta t}(Q_j - 2Q_{j-1} + Q_{j-2}) + \frac{\Gamma}{2}(Q_j - Q_{j-2}) + \Delta t\frac{\mathrm{d}}{\mathrm{d}Q_{j-1}}U(Q_{j-1}) \tag{C-3}$$

We have to emphasize here that eq C-3 is a result of direct recursion construction which has, however, some “degrees of freedom,” particularly in the last form. For example, Graham[57,58] used the following form:

$$\frac{1}{2}\left\{\frac{\mathrm{d}}{\mathrm{d}Q_j}U(Q_j) + \frac{\mathrm{d}}{\mathrm{d}Q_{j-1}}U(Q_{j-1})\right\} \tag{C-4}$$

This form of discretization was also considered in ref 33, where it has been shown that the discrepancy between final results is due to different representations of discrete forces. A thorough investigation of the problem of a unique form of discretization of a functional integral can be found in refs 59 and 60. Particularly, Schmid[60] has argued that the form C-3 is only appropriate for the path integral used in the probabilistic sense because of a requirement of zero path fluctuations at the terminal point. Meanwhile, we use expression C-3, but will come back to this point later.

The Jacobian eq 7 can now be calculated in a straightforward way as

$$\frac{\mathscr{D}F(t)}{\mathscr{D}Q(t)} = \det_{N\to\infty}\begin{pmatrix}\frac{\partial F_1}{\partial Q_1} & \frac{\partial F_1}{\partial Q_2} & \frac{\partial F_1}{\partial Q_3} & \ldots\\ \frac{\partial F_2}{\partial Q_1} & \frac{\partial F_2}{\partial Q_2} & \frac{\partial F_2}{\partial Q_{31}} & \ldots\\ \frac{\partial F_3}{\partial Q_1} & \frac{\partial F_3}{\partial Q_2} & \frac{\partial F_3}{\partial Q_3} & \ldots\\ \ldots & \ldots & \ldots & \ldots\end{pmatrix} = \mathrm{de}_{N\to\infty}$$

$$\begin{pmatrix}\frac{M}{\Delta t}\left(1+\frac{\Gamma\Delta t}{2M}\right) & 0 & 0 & 0 & \ldots\\ \Delta t\frac{\mathrm{d}2U}{\mathrm{d}Q_1^2} - \frac{2M}{\Delta t} & \frac{M}{\Delta t}\left(1+\frac{\Gamma\Delta t}{2M}\right) & 0 & 0 & \ldots\\ \frac{M}{\Delta t}\left(1-\frac{\Gamma\Delta t}{2M}\right) & \Delta t\frac{\mathrm{d}^2U}{\mathrm{d}Q_2^2} - \frac{2M}{\Delta t} & \frac{M}{\Delta t}\left(1+\frac{\Gamma\Delta t}{2M}\right) & 0 & \ldots\\ 0 & \frac{M}{\Delta t}\left(1-\frac{\Gamma\Delta t}{2M}\right) & \Delta t\frac{\mathrm{d}^2U}{\mathrm{d}Q_3^2} - \frac{2M}{\Delta t} & \frac{M}{\Delta t}\left(1+\frac{\Gamma\Delta t}{2M}\right) & \ldots\\ \ldots & \ldots & \ldots & \ldots & \ldots\end{pmatrix} = \left(\frac{M}{\Delta t}\right)^N\left(1+\frac{\Gamma\Delta t}{2M}\right)^N_{N\to\infty} \tag{C-5}$$

The main consequence of our calculations is a coordinate independence of the Jacobian eq C-5. However, it can be checked easily that this Jacobian would be coordinate dependent if we use another discretization of the forces (eq C-4). Although we believe this latter expression is not appropriate in our case, it will not be discussed here in detail because it is not crucial in this approach. Indeed, using the discretization C-4, we obtain the term coming from the potential that is of next order in Δt. In contrast with the overdamped case investigated in ref 33, this leads to a vanishing contribution to the action in the continuous path limit where, when $\Delta t \to 0$. We note here that the final result for the Jacobian becomes divergent when $\Delta t \to 0$, so that the question of final limit of path integral arises. This problem can be removed by a proper normalization of the integral in the continuum limit. We do not address this question in detail, since we are interested in the *relative* contributions of different path realizations.

Appendix D: Fokker–Planck Equation

To construct the Fokker–Planck equation (FPE) for the system governed by eqs 1 and 2, let us start with the exact master equation,[61]

$$\frac{\partial\mathscr{P}\{Q(t)\}}{\partial t} = \frac{\partial}{\partial t}\langle\delta(Q(t)-Q)(v(t)-v)\rangle \tag{D-1}$$

which, after some algebra, can be represented as

$$\begin{aligned}\frac{\partial\mathscr{P}\{Q(t)\}}{\partial t} = -v\frac{\partial\mathscr{P}\{Q(t)\}}{\partial Q} + \frac{dU(Q)}{dQ}\frac{\partial\mathscr{P}\{Q(t)\}}{\partial v} +\\ \Gamma\frac{\partial}{\partial v}(v\mathscr{P}\{Q(t)\}) + \frac{\partial^2}{\partial v\partial Q}\left\{\frac{D}{\tau}\int_0^t\mathrm{d}t'\exp\left(-\frac{|t-t'|}{\tau}\right)\right\langle\delta(Q(t)-\\ Q)(v(t)-v)\frac{\delta Q(t)}{\delta F(t')}\left.\right\rangle\left.\right\} + \frac{\partial^2}{\partial v^2}\left\{\frac{D}{\tau}\int_{0t}\mathrm{d}t'\right.\\ \exp\left(-\frac{|t-t'|}{\tau}\right)\left\langle\delta(Q(t)-Q)(v(t)-v)\frac{\delta v(t)}{\delta F(t')}\right\rangle\left.\right\}\end{aligned} \tag{D-2}$$

The angular brackets stand for the ensemble average, which can be done by the path integration,

$$\langle ... \rangle = \int \mathscr{D}F(t) ... \mathscr{P}\{F(t)\}$$

and $\delta Q(t)/\delta F(t')$ and $\delta v(t)/\delta F(t')$ are the corresponding functional derivatives. In fact, eq D-2 gives us nothing useful in comparison with the general relation (eq D-1), but it becomes meaningful if we work along the most probable path $\{Q_s(t), v_s(t)\}$, which is the solution of eq 14. In this case, the functional derivatives in eq D-2 can be taken out of the path integrals, and the remaining integration gives us precisely the probability density $\mathscr{P}\{Q_s(t)\}$. Going through this procedure, we come to the generalized Fokker−Planck equation

$$\frac{\partial \mathscr{P}\{Q_s(t)\}}{\partial t} = -v_s \frac{\partial \mathscr{P}\{Q_s(t)\}}{\partial Q_s} + \frac{\mathrm{d}U(Q_s)}{\mathrm{d}Q_s} \frac{\partial \mathscr{P}\{Q_s(t)\}}{\partial v_s} + \Gamma \frac{\partial}{\partial v_s}(v_s \mathscr{P}\{Q_s(t)\}) + \frac{\partial^2}{\partial v_s \partial Q_s}\{D_Q(Q_s)\mathscr{P}\{Q_s(t)\}\} + \frac{\partial^2}{\partial v^2}\{D_v(Q_s)\mathscr{P}\{Q_s(t)\}\} \quad \text{(D-3)}$$

where the generalized diffusion coefficients are defined as

$$D_Q(Q_s) = \frac{D}{\tau}\int_0^t \mathrm{d}t' \frac{\delta Q_s(t)}{\delta F(t')} \exp\left(-\frac{|t-t'|}{\tau}\right) \quad \text{(D-4)}$$

$$D_v(Q_s) = \frac{D}{\tau}\int_0^t \mathrm{d}t' \frac{\delta v_s(t)}{\delta F(t')} \exp\left(-\frac{|t-t'|}{\tau}\right) \quad \text{(D-5)}$$

Appendix E: Derivation and Analysis of Eq 15

After straightforward algebra, eq 6 can be reorganized as

$$S[Q(t)] = S_{cl}[Q(t)] + 2\Gamma J_1 + 2MJ_2 + \tau^2 J_3 + 2M\tau J_4 + 2\Gamma\tau J_5 \quad \text{(E-1)}$$

where $S_{cl}[Q(t)]$ is given by eq 16, and J_i are the integrals to be analyzed. The only requirement we use here is that the system is stationary at the reactant and product states. This means that the system starts and ends its evolution at the points where $U' = 0$ and whose coordinates and velocities at these points are time-independent. In this case,

$$J_1 = \int_0^t \mathrm{d}t\dot{Q}U' = U(Q_p) - U(Q_r) = \text{const} \quad \text{(E-2)}$$

so that this part can be excluded from the *classical* action.

$$J_2 = \int_0^t \mathrm{d}t\ddot{Q}U' = \left[\dot{Q}U' - \frac{\mathrm{d}}{\mathrm{d}t}U\right]\Big|_0^t \quad \text{(E-3)}$$

This is exactly zero if the potential does not depend on time explicitly;

$$J_3 = \int_0^t \mathrm{d}t(M\dddot{Q} + \Gamma\ddot{Q})^2 = \int_{\zeta_r}^{\zeta_p} \dot{\zeta}\mathrm{d}\zeta = \text{const} \quad \text{(E-4)}$$

where $\zeta = M\ddot{Q} + \Gamma\dot{Q}$. The last integral in eq E-4 must be constant because of Maupertuis' principle[62] in the space of variables ζ.

Let us rewrite the integrals J_4 and J_5 as

$$J_4 = \int_0^t \mathrm{d}t(\tau\dddot{Q} - \ddot{Q})\dot{Q}U'' = U'(\tau\dddot{Q} - \ddot{Q})|_0^t + \int_0^t \mathrm{d}t(\ddot{Q} - \tau\dddot{Q})U' \quad \text{(E-5)}$$

$$J_5 = \int_0^t \mathrm{d}t(\tau\ddot{Q} - \dot{Q})\dot{Q}U'' = U'(\tau\ddot{Q} - \dot{Q})|_0^t + \int_0^t \mathrm{d}t(\ddot{Q} - \tau\dddot{Q})U' \quad \text{(E-6)}$$

The first terms in both integrals turn out to be zero because of the condition $U' = 0$ at the initial and final states. However the last terms are path dependent and generally do contribute to the total action. Thus we come to formula 15 in the main body of the text.

References and Notes

(1) Berne, B. J.; Ciccotti, G.; Coker, D. F. Eds. *Classical and Quantum Dynamics in Condensed Phase Simulations*; World Scientific: Singapore, 1998.
(2) Elber, R.; Meller, J.; Olender, R. *J. Phys. Chem. B* **1999**, *103*, 899.
(3) Olender, R.; Elber, R. *J. Chem. Phys*. **1996**, *105*, 9299.
(4) Zaloj, V.; Elber, R. *Comput. Phys. Commun*. **2000**, *128*, 118.
(5) Elber, R.; Ghosh, A.; Cárdenas, A. *Acc. Chem. Res*. **2002**, *35*, 396.
(6) Bennet, C. H. In *Algorithms for Chemical Computations*; Christofferson, R. E., Ed.; ACS Symposium Series No. 46; American Chemical Society: Washington, D.C., 1977; p 63.
(7) Keck, J. *J. Chem. Phys*. **1960**, *32*, 1035.
(8) Anderson, J. B. *J. Chem. Phys*. **1973**, *58*, 4684.
(9) Chandler, D. *J. Chem. Phys*. **1978**, *68*, 2959.
(10) Melver, J.; Komornicki, A. *J. Am. Chem. Soc*. **1972**, *94*, 2625.
(11) Cerjan, C. J.; Miller, W. H. *J. Chem. Phys*. **1981**, *75*, 2800.
(12) Jensen, F. *J. Chem. Phys*. **1995**, *102*, 6706.
(13) Dellago, C.; Bolhuis, P. G.; Csajka, F. S.; Chandler, D. *J. Chem. Phys*. **1998a**, *108*, 1964.
(14) Dellago, C.; Bolhuis, P. G.; Chandler, D. *J. Chem. Phys*. **1998b**, *108*, 9236.
(15) Csajka, F. S.; Chandler, D. *J. Chem. Phys*. **1998**, *109*, 1125.
(16) Bolhuis, P. G.; Dellago, C.; Chandler, D. *Faraday Discuss. Chem. Soc*. **1998**, *110*, 421.
(17) Dellago, C.; Bolhuis, P. G.; Chandler, D. *J. Chem. Phys*. **1999**, *110*, 6617.
(18) Geissler, P. L.; Dellago, C.; Chandler, D. *Phys. Chem. Chem. Phys*. **1999**, *1*, 1317.
(19) Martí, J.; Csajka, F. S.; Chandler, D. *Chem. Phys. Lett*. **2000**, *328*, 169.
(20) Ying, S. C. *Phys. Rev. B* **1990**, *41*, 7068.
(21) Ala-Nissila, T.; Ying, S. C. *Prog. Surf. Sci*. **1992**, *39*, 227.
(22) Ala-Nissila, T.; Ferrando, R.; Ying, S. C. *Adv. Phys*. **2002**, *51*, 949.
(23) Grote, R. F.; Hynes, J. T. *J. Chem. Phys*. **1980**, *73*, 2715.
(24) Grote, R. F.; Hynes, J. T. *J. Chem. Phys*. **1982**, *77*, 3736.
(25) Kramers, H. A. *Physica (The Hague)* **1940**, *7*, 284.
(26) Hänggi, P.; Talkner, P.; Borkovec, M. *Rev. Mod. Phys*. **1990**, *62*, 251.
(27) Frishman, A. M.; Pollak, E. *J. Chem. Phys*. **1993**, *98*, 9532.
(28) Haynes, G. R.; Voth, G. A. *J. Chem. Phys*. **1995**, *103*, 10176.
(29) Horsthemke, W.; Lefever, R. *Noise-Induced Transitions, Theory and Applications in Physics, Chemistry, and Biology*; Springer-Verlag: Berlin, 1984.
(30) Pratt, L. R. *J. Chem. Phys*. **1986**, *85*, 5045.
(31) Cai, W.; Kalos, M. H.; de Koning, M.; Bulatov, V. V. *Phys. Rev. E* **2002**, *66*, 046703.
(32) de Koning, M.; Cai, W.; Sadigh, B.; Oppelstrup, T.; Kalos, M. H.; Bulatov, V. V. *J. Chem. Phys*. **2005**, *122*, 074103.
(33) Elber, R.; Shalloway, D. *J. Chem. Phys*. **2000**, *112*, 5539.
(34) Huo, S.; Straub, J. *J. Chem. Phys*. **1997**, *107*, 5000.
(35) Elber, R.; Karplus, M. *Chem. Phys. Lett*. **1987**, *139*, 375.
(36) Press, W. H.; Teukolsky, S. A.; Vetterling, W. T.; Flannery, B. P. *Numerical Recipes: The Art of Scientific Computing*; Cambridge University Press: Cambridge, 1992.
(37) Rowan, T. Functional Stability Analysis of Numerical Algorithms. Ph.D. Thesis, Department of Computer Sciences, University of Texas at Austin, 1990.
(38) Bergsma, J. P.; Gertner, B. J.; Wilson, K. R.; Hynes, J. T. *J. Chem. Phys*. **1987**, *86*, 1356.
(39) Gertner, B. J.; Wilson, K. R.; Hynes, J. T. *J. Chem. Phys*. **1989**, *90*, 3537.
(40) Chandrasekhar, J.; Smith, S. F.; Jorgensen, W. L. *J. Am. Chem. Soc*. **1984**, *106*, 3049.
(41) Chiles, R. A.; Rossky, P. J. *J. Am. Chem. Soc*. **1984**, *106*, 6867.
(42) Chandrasekhar, J.; Smith, S. F.; Jorgensen, W. L. *J. Am. Chem. Soc*. **1985**, *107*, 154.
(43) Ciccotti, G.; Ferrario, M.; Hynes, J. T.; Kapral, R. *J. Chem. Phys*. **1990**, *93*, 7137.
(44) Ise, N.; Okubo, T.; Kunugi, S. *Acc. Chem. Res*. **1982**, *15*, 171.
(45) Bender, M. L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins*; Wiley: New York, 1971.
(46) Perutz, M. F. *Science* **1978**, *201*, 1187.

(47) Alber, T. *Annu. Rev. Biochem*. **1989**, *58*, 765.

(48) Moss, F., McClintock, P. V. E., Eds. *Noise in Nonlinear Dynamical Systems*; Cambridge University Press: New York, 1989.

(49) Zhu, S. B.; Lee, J.; Robinson, G. W. *J. Phys. Chem*. **1988**, *92*, 2401.

(50) Wu, X. G.; Kapral, R. *J. Chem. Phys*. **1989**, *91*, 5528.

(51) Mori, H. *Prog. Theor. Phys*. **1965**, *33*, 423.

(52) Wahnström, G. *Phys. Rev. B* **1986a**, *33*, 1020.

(53) Wahnström, G. *J. Chem. Phys*. **1986b**, *84*, 5931.

(54) Kapral, R.; Consta, S.; McWhirter, L. In *Classical and Quantum Dynamics in Condensed Phase Simulations*; Berne, B. J., Ciccotti, G., Coker, D. F., Eds.; World Scientific: Singapore, 1998.

(55) Kubo, R. *Rep. Prog. Phys*. **1966**, *29*, 255.

(56) McKane, A. J.; Luckock, H. C.; Bray, A. J. *Phys. Rev. A* **1990**, *41*, 644.

(57) Graham, R. In *Springer Tracts in Modern Physics*; Springer-Verlag: New York, 1973; Vol. 66.

(58) Graham, R. In *Fluctuations*, *Instabilities and Phase Transitions*; Riste, T. Ed.; Plenum: New York, 1975.

(59) Leschke, H.; Schmutz, M. *Z. Phys. B* **1977**, *27*, 85.

(60) Schmid, A. *J. Low Temp. Phys*. **1982**, *49*, 609.

(61) Risken, H. *The Fokker-Planck Equation: Methods of Solution and Applications*; Springer-Verlag: Berlin, 1984.

(62) Arnold, V. I. *Mathematical Methods of Classical Mechanics*; Springer-Verlag: New York, 1978.