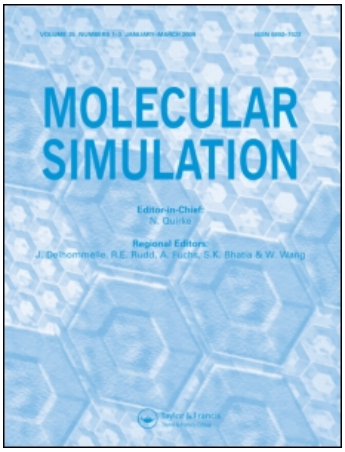

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Blue Moon Approach to Rare Events

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The "Blue Moon" ensemble is a computationally efficient molecular dynamics method to estimate the rate constants of rare activated events when the process can be described by a reaction coordinate $\xi(r)$, a well-defined function in configuration space. By means of holonomic constraints a number of values of $\xi(r)$ can be prescribed along the relevant path to identify the "bottleneck" region first and to sample an ensemble of starting conditions to generate activated trajectories. These MD trajectories sample phase space according to a biased configurational distribution. With a suitable re-weighting of averages from such ensemble of trajectories one can characterize completely rare events.

Keywords: Blue moon approach; Rare events; Reactive flux correlation; MD trajectories

INTRODUCTION

Rare events are activated processes in which a transition takes place between two stable states, i.e. states where the system spends the overwhelming majority of its time. Stable states are separated by a region of very low probability so that the transition can be viewed as the infrequent crossing of a free energy barrier much higher than k_BT. As such, the transition is of very short duration compared with the time one has to wait for it to occur and cannot be simulated using conventional techniques.

For a classical system, described by an Hamiltonian $\mathcal{H}(\mathbf{r}^{\mathcal{N}}, \mathbf{p}^{\mathcal{N}}) = \mathcal{K} + \mathcal{V}$ whose time evolution can be viewed as a curve in the $6N$-dimensional phase space identified by the initial conditions and generated according to the equations of motion $\dot{\mathbf{r}} = (\partial\mathcal{H}/\partial\mathbf{p})$, $\dot{\mathbf{p}} = -(\partial\mathcal{H}/\partial\mathbf{r})$, the transition state can be identified when a property $\xi = \xi(\mathbf{r}^N)$ exists which takes the corresponding value $\xi^\ddagger$ and otherwise fluctuates between the values ξ_A and ξ_B corresponding to the reactant and product states, respectively. Escape from the region around $\xi = \xi^\ddagger$ is fast. See Fig. 1 for a pictorial interpretation.

In order to give a Statistical Mechanics description of rare events we start from the Boltzmann's definition of probability for a state identified by a particular value $\xi = \xi'$, introducing the reversible work $W_\xi(\xi')$ (free energy) associated to the "progress variable" $\xi(\mathbf{r}^N)$:

$$\mathcal{P}_\xi(\xi') = \langle\delta(\xi(\mathbf{r}^N) - \xi')\rangle \equiv C\exp\{-\beta W_\xi(\xi')\} \quad (1)$$

where $\langle\ldots\rangle$ is the canonical ensemble average with $\beta = (k_BT)^{-1}$. The constant C is determined by the normalization condition on $P(\xi)$. A typical behavior of $W_\xi(\xi')$ is sketched in Fig. 2.

The quantities of physical interest in rare events (chemical reactions) are the rate constants, for example, the one related to the population of the reactant which goes to the product state. In terms of the progress variable (reaction coordinate), the population of the reactant is given by the space function $\theta(\xi(\mathbf{r}^N) - \xi^\ddagger)$ with its associated flux $\dot{\theta} = \dot{\xi}\delta(\xi(\mathbf{r}^N) - \xi^\ddagger)$. Using the standard linear response theory approach for "transport" properties [1–3], for a review see also Refs. [4,5], one finds the analogous of a Green-Kubo formula for the rate constant k_f of the activated processes

$$k_f(t) = \frac{\langle\dot{\xi}\delta(\xi - \xi^\ddagger)\theta(\xi(t) - \xi^\ddagger)\rangle}{\langle\theta(\xi^\ddagger - \xi)\rangle}, \quad (2)$$

Given that $\xi = \xi^\ddagger$ is a rare event and happens very infrequently it is difficult, if not impossible, to collect

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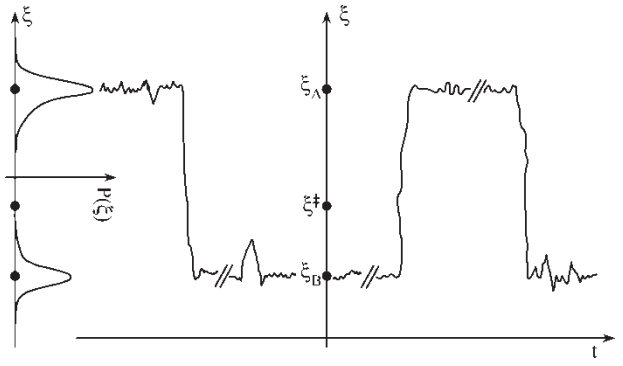

FIGURE 1 A typical dynamical evolution of the reaction coordinate $\xi(t)$, characterized by transition of very short duration between values close to ξ_A or ξ_B, that identify the two stable states around which the systems spend the majority of its time as expressed by the two maxima of $P(\xi)$, the probability distribution along ξ, pictured on the left.

good statistics for the rate constants by "brute force" molecular dynamics simulation. Special methods have to be used to determine the probability of a highly improbable value of ξ. They include special sampling schemes, for example umbrella sampling [6], to compute free energy differences $W(\xi') - W(\xi)$. The rate constant in turn can be computed, knowing this probability, as the product of the $P(\xi^\ddagger)$ and the average fraction of trajectories which, starts at the transition point $\xi^\ddagger$ and end in the product region. The classical treatment of chemical reactions we have just described was first introduced by Keck [7,8] and Anderson [9] to treat gas phase chemical reactions and later applied by Bennett [10,11] and Chandler [2] for the treatment of condensed-phase rate processes.

In this paper, we discuss a particular sampling scheme which enhances the statistical occurrence of highly improbable values of the reaction coordinate (i.e. a function of the whole set of particle coordinates) by fixing it to any desired value ξ' through the holonomic constraints $\xi(\mathbf{r}^N) = \xi'$. Historically, holonomic constraints could be first introduced in Molecular Dynamics (MD) simulations [12], in place of stiff restoring forces, to model strong chemical bonds which are not to be broken during the simulation, only because of the availability of a suitable algorithm. Thus it became possible to integrate efficiently the dynamics and simulate molecular systems composed of large molecules. However, the use of holonomic constraints is not restricted to the modeling of molecular systems, but naturally arises in other situations such as, for example, the Car-Parrinello *ab-initio* [13–15], where one has to satisfy orthonormality conditions for the electronic orbitals contributing to the electron density of the system, or, for the case of interest here, when holonomic constraints can be shown to be a useful tool to frequently produce rare events in molecular dynamics simulations. In particular, we refer to the approach known as the Blue Moon ensemble [16,17], which is not restricted to the computation of static equilibrium properties (free energies) related to activated processes but has been generalized to include the full calculation of dynamic properties such as the rate constants.

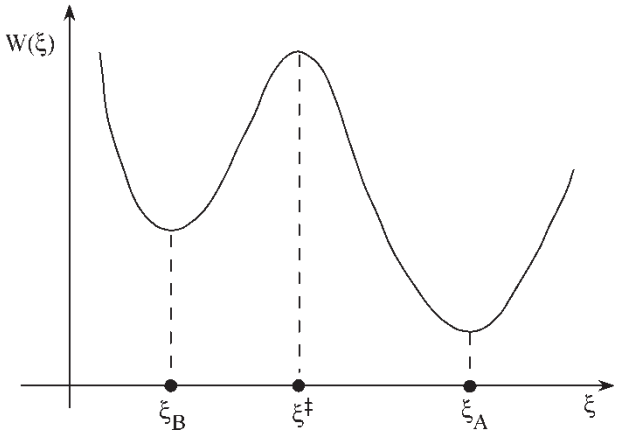

FIGURE 2 The potential of mean force $W(\xi)$ corresponding system whose behaviour was sketched in Fig. 1.

In order to solve the statistical problem we use the following steps: (i) rewriting the expression for the rate constants in terms of conditional averages and (ii) establishing a theorem that states that (infrequent) conditional averages can be estimated by corresponding "constrained" averages with good statistics at relatively low computational prices.

REACTIVE FLUX CORRELATION FORMULAS

We begin this section by recalling the autocorrelation function expressions for the rate constant of a reaction. These expressions were first derived by Yamamoto [1] in 1960 and have continued to fascinate researchers in the area as evidenced by the number of times they have been rederived and reinterpreted in the literature [2,3,18–21].

In order to give a statistical mechanical definition of the rate of the reaction

$$A \rightleftharpoons B, \tag{3}$$

we must first introduce a microscopic definition of the chemical species A and B. This is achieved by using the progress variable ξ and defining the states corresponding to species A such that $\xi < \xi^\ddagger$ while the complementary range defines species B. The dividing surface between the two species, $\xi = \xi^\ddagger$, identifies the rare value of ξ which must be crossed when transforming A to B (or vice versa). The microscopic variable

$$\hat{n}_A(\xi) = \theta(\xi^\ddagger - \xi(\mathbf{r}^N)) = \begin{cases} 1 & \xi < \xi^\ddagger \\ 0 & \xi > \xi^\ddagger \end{cases} \tag{4}$$

characterizes microscopically the species A ($n_A = \langle \hat{n}_A \rangle$, as usual) while

$$\dot{\hat{n}}_A(\xi) = -\dot{\xi}\delta(\xi^\ddagger - \xi) \tag{5}$$

is the microscopic expression for its flux.

If a phenomenological law is valid, one can write down a rate equation for the reaction and identify the forward and reverse rate coefficient, k_f and k_r, respectively.

By applying the fluctuation–dissipation theorem one finds that the rate coefficient, say k_f, can be computed in microscopic terms from the plateau value of the quantity $k_f(t)$ defined by Refs. [1,2]

$$\begin{aligned} k_f(t) &= \frac{1}{n_A}\int_0^t \langle \dot{\hat{n}}_A(\xi)\dot{\hat{n}}_A(\xi(t'))\rangle \, dt' \\ &\equiv -\frac{1}{n_A}\langle \dot{\xi}\delta(\xi - \xi^\ddagger)\theta(\xi^\ddagger - \xi(t))\rangle \\ &= \frac{\langle \dot{\xi}\delta(\xi - \xi^\ddagger)\theta(\xi(t) - \xi^\ddagger)\rangle}{\langle \theta(\xi^\ddagger - \xi)\rangle}, \end{aligned} \tag{6}$$

where the last equality follows by observing that $\theta(\xi^\ddagger - \xi(t)) = 1 - \theta(\xi(t) - \xi^\ddagger)$ and that $< \dot{\xi}\delta(\xi - \xi^\ddagger) >= 0$. The limit $t \to 0_+$ of Eq. (6) plays a special role in the theory since it gives the transition state theory value for the rate constant [22]

$$\begin{aligned} k_f^{TST} &= -\frac{1}{n_A}\langle \dot{\xi}\theta(-\dot{\xi})\delta(\xi - \xi^\ddagger)\rangle \\ &= \frac{\langle \dot{\xi}\theta(\dot{\xi})\delta(\xi - \xi^\ddagger)\rangle}{\langle \theta(\xi^\ddagger - \xi)\rangle}, \end{aligned} \tag{7}$$

where the last equality follows by time reversal invariance. k_f^{TST} is the reference value for most elementary treatments of the rate constant. We can separate the static and dynamic contributions to the rate constant by multiplying and dividing the right hand side of Eq. (6) by $\langle \delta(\xi - \xi^\ddagger)\rangle$. We then obtain

$$\begin{aligned} k_f(t) &= \frac{1}{n_A^{eq}}\langle \delta(\xi - \xi^\ddagger)\rangle \left[\frac{\langle \dot{\xi}\delta(\xi - \xi^\ddagger)\theta(\xi(t) - \xi^\ddagger)\rangle}{\langle \delta(\xi - \xi^\ddagger)\rangle}\right] \\ &= \frac{1}{\langle \theta(\xi^\ddagger - \xi)\rangle} \times C\exp\{-\beta W_\xi(\xi^\ddagger)\} \\ &\quad \times \frac{\langle \dot{\xi}\delta(\xi - \xi^\ddagger)\theta(\xi(t) - \xi^\ddagger)\rangle}{\langle \delta(\xi - \xi^\ddagger)\rangle} \quad = \frac{1}{\int_{\xi<\xi^\ddagger} d\xi' \langle \delta(\xi - \xi')\rangle} \\ &\quad \times \exp\left\{-\beta \int_{\text{reference}}^{\xi^\ddagger} d\xi' \frac{\langle \partial\mathcal{H}/\partial\xi')\delta(\xi - \xi')\rangle}{\langle \delta(\xi - \xi')\rangle}\right\} \\ &\quad \times \frac{\langle \dot{\xi}\delta(\xi - \xi^\ddagger)\theta(\xi(t) - \xi^\ddagger)\rangle}{\langle \delta(\xi - \xi^\ddagger)\rangle} \end{aligned} \tag{8}$$

In this way we have explicitly introduced the reversible work needed to bring the system from some reference state to ξ':

$$W(\xi') = -k_B T \ln \mathcal{P}_\xi(\xi'), \tag{9}$$

with

$$\mathcal{P}_\xi(\xi') = \frac{1}{Q}\int d\mathbf{r}^N d\mathbf{p}^N \exp\{-\beta\mathcal{H}\}\delta(\xi(\mathbf{r}^N) - \xi'). \tag{10}$$

Indeed, if we try to obtain $P_\xi(\xi')$ via thermodynamic integration, immediately we see that the reversible work is given by

$$\begin{aligned} W(\xi) &= \int^\xi d\xi' \frac{dW(\xi')}{d\xi'} \\ &= \int^\xi d\xi' \frac{\langle -\frac{\partial\mathcal{H}}{\partial\xi}\delta(\xi(\mathbf{r}^N) - \xi')\rangle}{\langle \delta(\xi(\mathbf{r}^N) - \xi')\rangle} \end{aligned} \tag{11}$$

i.e. $W(\xi)$ is the potential of mean force associated with the conditional average of the generalized force $F_\xi = -(\partial\mathcal{H})/(\partial\xi)$. Note that to derive this simple result we have to go through a change of variables in the statistical mechanical derivation: from $\{\mathbf{r}^N, \mathbf{p}^N\}$ to $\{\mathbf{u}, \mathbf{p}^u\} = \{\xi, \mathbf{q}, p^\xi, \mathbf{p}^q\}$. Explicitly, in terms of the Jacobian matrix of the transformation $J_{i\alpha} = (\partial r_i/\partial u_\alpha)$ and the metric matrix $\mathbf{M}$

$$\mathbf{M}_{\alpha\beta} = \sum_i m_i \frac{\partial \mathbf{r}_i}{\partial u_\alpha}\frac{\partial \mathbf{r}_i}{\partial u_\beta} = (\mathbf{J}^T \boldsymbol{\mu}\mathbf{J})_{\alpha\beta}, \quad \mu_{ij} = \delta_{ij}m_i \tag{12}$$

for a system of N particles interacting through the potential $V_N(\mathbf{r}_1, \ldots, \mathbf{r}_N)$ the effective mean force can be computed in terms of the matrix determinants as

$$\begin{aligned} \frac{dW}{d\xi'} &= \frac{1}{\langle \delta(\xi - \xi')\rangle}\int d\mathbf{r}^N \delta(\xi - \xi')\exp(-\beta V_N) \\ &\quad \times \frac{\partial}{\partial\xi}\left[V_N - \frac{1}{2}k_B T \ln|\mathbf{M}|\right] \\ &= \frac{1}{\langle \delta(\xi - \xi')\rangle}\int d\mathbf{r}^N \delta(\xi - \xi') \\ &\quad \times \exp(-\beta V_N)\sum_i \frac{\partial \mathbf{r}_i}{\partial\xi}\cdot\frac{\partial}{\partial \mathbf{r}_i}[V_N + k_B T \ln|\mathbf{J}^{-1}|] \end{aligned} \tag{13}$$

where one needs to compute explicitly both the Jacobian of the transformation and the vectors $(\partial \mathbf{r}_i/\partial\xi)$ in order to perform the differentiation with respect to ξ.

CONSTRAINTS AND BLUE MOON ENSEMBLE

The question now is: how can we obtain good statistics from a MD simulation for a conditional average when the conditioning value we are interested is very infrequent? A very natural answer is to use the infrequent value of the reaction coordinate as a holonomic constraint, $\xi(\mathbf{r}^N) = \xi^\ddagger$, in the simulation and to unbias the sampling along the constrained trajectory by using the relations between constrained and unconstrained ensembles [16,23].

In Molecular Dynamics, a configurational conditional average

$$O_{\rm cond} = \frac{\langle \hat{O}(\mathbf{r}^N)\delta(\xi(\mathbf{r}^N) - \xi')\rangle}{\langle \delta(\xi(\mathbf{r}^N) - \xi')\rangle} \tag{14}$$

can be computed by using an alternative trajectory, with $\xi(\mathbf{r}^N)$ constrained to be equal to ξ' and performing the unbiased average

$$O_{\rm cond} = \frac{\langle Z^{-\frac{1}{2}}\hat{O}(\mathbf{r}^N)\rangle_{\xi'}}{\langle Z^{-\frac{1}{2}}\rangle_{\xi'}}, \quad Z = \sum_i \frac{1}{m_i}\left(\frac{\partial\xi}{\partial\mathbf{r}_i}\right)^2 \tag{15}$$

where it appears a reasonably-simple-to-compute unbiasing factor, originated by the metric factor related to the momenta integration on the hypersurface determined by the constraints in phase space. The effective mean force in Eq. (13) can now be expressed after some algebra [16,23] by the constrained average

$$\begin{aligned}\frac{{\rm d}W}{{\rm d}\xi'} &= \frac{\left\langle Z^{-\frac{1}{2}}\frac{\partial\mathcal{H}}{\partial\xi}\right\rangle_{\xi'}}{\langle Z^{-\frac{1}{2}}\rangle_{\xi'}} \\ &= \frac{\left\langle Z^{-\frac{1}{2}}\frac{\partial}{\partial\xi}\left[V_N - k_BT\ln(|\mathbf{J}|Z^{\frac{1}{2}})\right]\right\rangle_{\xi'}}{\langle Z^{-\frac{1}{2}}\rangle_{\xi'}}\end{aligned} \tag{16}$$

Again to use this results one has to make explicit the coordinate transformation with its Jacobian determinant and the vectors needed to differentiate with respect to ξ in the configuration space.

Instead of this "brute force" approach, an alternative, simpler way, has been proposed [24] on the basis of the equations of motion written for the generalized coordinates $\{\mathbf{u}, \mathbf{p}^u\}$ where one has, in turn, to consider explicitly the Lagrangian multiplier λ associated to the constraint on ξ

$$\dot{\mathbf{u}} = \frac{\partial\mathcal{H}}{\partial\mathbf{p}^u}, \tag{17}$$

$$\dot{\mathbf{p}}^u = -\frac{\partial\mathcal{H}}{\partial\mathbf{u}} - \lambda\delta_{\xi\mathbf{u}}.$$

As can be seen from Eq. (13), the difficulty was brought about when performing integration over the momenta. We could instead try to keep the momentum-dependent observable $(\partial\mathcal{H})/(\partial\xi)$ and explicitly compute the difference between the configurationally unbiased constrained average of our quantity and the corresponding conditional average. Remembering that the transformations $\{\mathbf{r}^N, \mathbf{p}^N\} \leftrightarrow \{\mathbf{u}, \mathbf{p}^u\}$ is canonical and that the value of the Lagrangian multiplier appearing in our equations is independent of the chosen coordinates (this can be demonstrated by a tiring but otherwise straightforward calculation [24]) after some Gaussian integrations, the effective force can be rewritten as

$$\frac{{\rm d}W}{{\rm d}\xi'} = \frac{\left\langle Z^{-\frac{1}{2}}\left(-\lambda - \dot{p}_\xi + \frac{k_BT}{2}\frac{\partial\ln Z}{\partial\xi}\right)\right\rangle_{\xi'}}{\langle Z^{-\frac{1}{2}}\rangle_{\xi'}} \tag{18}$$

where the first term is a quantity known along a simulation, and easy to compute, while the rest has still to be simplified. Observing that by time reversal symmetry the average value of a total derivative is zero, one can rewrite

$$\begin{aligned}\langle Z^{-\frac{1}{2}}\dot{p}^\xi\rangle_{\xi'} &= \left\langle\frac{\rm d}{{\rm d}t}[Z^{-\frac{1}{2}}p^\xi]\right\rangle_{\xi'} - \left\langle\left[\frac{\rm d}{{\rm d}t}Z^{-\frac{1}{2}}\right]p^\xi\right\rangle_{\xi'} \\ &= \frac{1}{2}\left\langle Z^{-\frac{1}{2}}\left(\frac{1}{Z}\frac{\partial Z}{\partial\mathbf{u}}\right)\cdot\dot{\mathbf{u}}p^\xi\right\rangle_{\xi'} \\ &= -\langle Z^{-\frac{1}{2}}k_BT\mathcal{G}\rangle_{\xi'} + \left\langle Z^{-\frac{1}{2}}\frac{k_BT}{2}\frac{\partial\ln Z}{\partial\xi}\right\rangle_{\xi'},\end{aligned} \tag{19}$$

with the observable $\mathcal{G}$ a completely explicit quantity defined by

$$\mathcal{G} = \frac{1}{Z^2}\sum_{i,j=1}^{N}\frac{1}{m_im_j}\frac{\partial\xi}{\partial\mathbf{r}_i}\cdot\frac{\partial^2\xi}{\partial\mathbf{r}_i\partial\mathbf{r}_j}\cdot\frac{\partial\xi}{\partial\mathbf{r}_j}. \tag{20}$$

Recombining all terms together we finally find

$$\mathcal{F}_{\xi'} = \frac{\langle -\frac{\partial\mathcal{H}}{\partial\xi}\delta(\xi - \xi')\rangle}{\langle\delta(\xi - \xi')\rangle} = \frac{\langle Z^{-\frac{1}{2}}[\lambda + k_BT\mathcal{G}]\rangle_{\xi'}}{\langle Z^{-\frac{1}{2}}\rangle_{\xi'}}, \tag{21}$$

the sought for expression containing no implicit quantities and using the constraint forces which are automatically provided by SHAKE [25].

Three comments are in order. First, the Lagrangian multiplier λ appearing in the above equations is exactly the same in the cartesian equations of motion. Second, in a previous work, Frenkel and Ruiz [26] have found on a sound physical basis, although not completely general mathematically, a closely related result which also permits one to avoid the definition of the other coordinates $\mathbf{q}$ and to compute explicitly both $|J|$ and $(\partial/\partial\xi)$. Finally notice that the simplification occurs when using the constraint forces. The expression using the generalized force $(\partial\mathcal{H})/(\partial\xi)$ in the constrained ensemble is still implicit and complex. The idea to use the constraint force to simplify the calculation of the reversible work has been put forward by Mulders *et al.* [27]. However, these authors have forgotten that constrained averages have to be unbiased since the reversible work is not directly related to constrained averages but only to conditional ones.

TIME CORRELATION FUNCTIONS BY BLUE MOON ENSEMBLE

As already recalled in section "Reactive Flux Correlation Formulas", the two quantities relevant to the understanding of activated processes are the reversible work (a time-independent quantity) and time correlation functions of the form,

$$C_{\xi'}(t)=\frac{\langle \mathcal{O}(\mathbf{r}^N(0),\mathbf{p}^N(0))\mathcal{O}(\mathbf{r}^N(t),\mathbf{p}^N(t))\delta(\xi(\mathbf{r}^N(0))-\xi')\rangle}{\langle \delta(\xi(\mathbf{r}^N(0))-\xi')\rangle}, \tag{22}$$

(the transmission coefficient in chemical reactions is typically of this form). When $\xi(\mathbf{r}^N)=\xi'$ is a rare event these quantities are very difficult to obtain for exactly the same reasons that occur in the calculation of the reversible work. Furthermore, we now need to integrate the real dynamics of the system and not the constrained one. These difficulties can be overcome by sampling independently initial conditions from the appropriate ensemble, instead of using points along a dynamical trajectory, and then integrating the correct dynamics for the (short) times needed to be followed to construct the relevant correlation functions. This is what we call the Gibbs definition of time correlation functions:

$$\begin{aligned}\langle \mathcal{O}(0;\mathbf{r}^N,\mathbf{p}^N)&\delta(\xi(0;\mathbf{r}^N)-\xi')\mathcal{O}(t;\mathbf{r}^N,\mathbf{p}^N)\rangle\\ &=\frac{1}{Q}\int d\mathbf{r}^N d\mathbf{p}^N \exp\{-\beta\mathcal{H}(\mathbf{r}^N,\mathbf{p}^N)\}\\ &\quad\times\mathcal{O}(\mathbf{r}^N,\mathbf{p}^N)\delta(\xi(\mathbf{r}^N,\mathbf{p}^N)-\xi')\\ &\quad\times[\mathcal{U}(t,0)\mathcal{O}(\mathbf{r}^N,\mathbf{p}^N)],\end{aligned} \tag{23}$$

where $\mathcal{U}(t,0)$ is the evolution operator of the system from time 0 to time t. This should be contrasted with the Boltzmann definition

$$\begin{aligned}&\langle \mathcal{O}(0;\mathbf{r}^N,\mathbf{p}^N)\mathcal{O}(t;\mathbf{r}^N,\mathbf{p}^N)\rangle\\ &=\lim_{\mathcal{T}\to\infty}\frac{1}{\mathcal{T}}\int_0^{\mathcal{T}} d\tau\,\mathcal{O}(\tau;\mathbf{r}^N,\mathbf{p}^N)\mathcal{O}(t+\tau;\mathbf{r}^N,\mathbf{p}^N).\end{aligned} \tag{24}$$

What we have to do then, is to sample correctly initial positions and momenta corresponding to the infrequent value of the reaction coordinate. This can be done extracting a sample of space configurations, corrected for the unbias factor $Z^{-\frac{1}{2}}$, from a trajectory constrained to satisfy the "rare" value ξ' and sampling the momenta from the unbiased velocity distribution and, then, integrating the full (unconstrained) dynamics starting from these initial conditions (see Fig. 3). Looking at Eq. (24) we see that, since we use the full unconstrained evolution operator $\mathcal{U}(t,0)$, if the initial conditions are properly chosen, our procedure is correct. To formalize the argument a bit more, let us now formulate in statistical terms the choice of the sample of initial conditions. We have to sample from the distribution

FIGURE 3 Schematic representation of Blue Moon sampling. The bold line represents the constrained ($\xi(r)=\xi'$) dynamical evolution in phase space. Open circles represent common points in configuration space which are the initial conditions of the activated trajectory sampling. Note that these points are not real crossings in phase space since the two trajectories differ in the momentum space. The dynamics represented by the light lines in the vicinity of the crossing points gives the dynamical information needed in Eq. (28).

$$P(\mathbf{r}^N,\mathbf{p}^N)\delta(\xi(\mathbf{r}^N)-\xi')=\frac{1}{Q}\exp\{-\beta\mathcal{H}(\mathbf{r}^N,\mathbf{p}^N)\} \tag{25}$$

$$\delta(\xi(\mathbf{r}^N)-\xi')=P_r(\mathbf{r}^N)P_p(\mathbf{p}^N|\mathbf{r}^N)\delta(\xi(\mathbf{r}^N)-\xi'),$$

where $P_r(\mathbf{r}^N)\propto\exp\{-\beta\mathcal{V}_N(\mathbf{r}^N)\}$ and $P_p(\mathbf{p}^N|\mathbf{r}^N)$ does not depend on $\mathbf{r}^N$ and is a simple product of Maxwellians. Since ξ' is infrequent we are sampling

$$P_{\xi'}(\mathbf{r}^N)\propto Z^{\frac{1}{2}}\exp\{-\beta\mathcal{V}_N(\mathbf{r}^N)\}\delta(\xi(\mathbf{r}^N)-\xi'). \tag{26}$$

We disregard $P_{\xi'}(\mathbf{p}^N|\mathbf{r}^N)$ and we sample $\mathbf{p}^N$ from $P_p(\mathbf{p}^N)$. Multiplying the probability used by $Z^{-\frac{1}{2}}$, we obtain as probability distribution

$$Z^{-\frac{1}{2}}P_{\xi'}(\mathbf{r}^N)P_p(\mathbf{p}^N)\propto P(\mathbf{r}^N,\mathbf{p}^N)\delta(\xi(\mathbf{r}^N)-\xi'), \tag{27}$$

which is proportional to the correct one. This is what we call the Blue Moon ensemble, from which

$$\begin{aligned}&\frac{\langle \mathcal{O}(0;\mathbf{r}^N,\mathbf{p}^N)\mathcal{O}(t;\mathbf{r}^N,\mathbf{p}^N)\delta(\xi(0;\mathbf{r}^N)-\xi')\rangle}{\langle \delta(\xi(0;\mathbf{r}^N)-\xi')\rangle}\\ &=\frac{\langle Z^{-\frac{1}{2}}\mathcal{O}(0;\mathbf{r}^N,\mathbf{p}^N)\mathcal{O}(t;\mathbf{r}^N,\mathbf{p}^N)\rangle_{\text{Blue Moon}}}{\langle Z^{-\frac{1}{2}}\rangle_{\text{Blue Moon}}}.\end{aligned} \tag{28}$$

Equation (28) extends the theorem in Eq. (15) to dynamical properties. Practically, what is required is to take an average over a Blue Moon ensemble of initial conditions of trajectories propagated by following the free time evolution of the system after release of the constraint ξ (see Fig. 3 and Ref. [28] for a specific application in the case of the ion dissociation reaction).

A MORE GENERAL CASE AND CONCLUSIONS

In the most interesting cases, the "true" reaction coordinate is far from being a well known expression in terms of the cartesian coordinates of the system. A more exploratory attitude is really needed to investigate the behavior of the reversible work

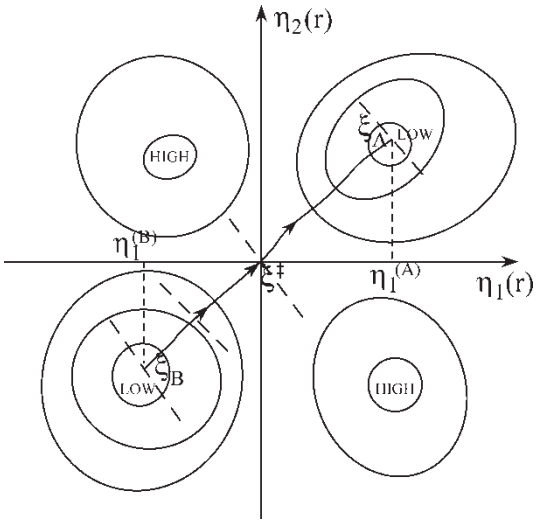

FIGURE 4 A multidimensional reaction coordinate space with two minima identified by ξ_A and ξ_B and separated by a region of high free energy. The minimum free energy path defining the reaction coordinate ξ is shown together with its orthogonal planes at specific points.

function. One possibility is to set up an "order parameter" space of small dimension L and construct in it a free energy (hyper)surface to locate both the transition state and the path defining the reaction coordinate as a function of the L variables $(\eta_1, \eta_2, \ldots, \eta_L)$. Keeping notation short, let us use $L = 2$ and name the two order parameters $\eta_1(\mathbf{r}^N)$ and $\eta_2(\mathbf{r}^N)$. The reversible work $W(\eta_1, \eta_2)$ can be expressed as a conditional average

$$W(\eta_1', \eta_2') = -k_B T \ln P(\eta_1', \eta_2') = -k_B T \ln \langle \delta(\eta_1 - \eta_1')\delta(\eta_2 - \eta_2') \rangle \quad (29)$$

In Fig. 4, a graphical solution is given for an imaginary case in which the use of a single coordinate, say η_1 is not sufficient to describe the rare events. Here, one needs to compute the values of the reversible work function W on enough points in the (η_1, η_2) plane to compute the contour lines and locate the transition state. The reaction path in the drawing is nothing but the graphical rendering of the "reaction coordinate" $\xi = \xi(\eta_1, \eta_2) = \xi(\mathbf{r}^N)$. In order to tackle such a case, the Blue Moon approach we sketched in the previous sections needs to be generalized to a multidimensional case. The full derivation is given by Sergi *et al.* [29] in the simple case when there are no molecular constraints involving the same cartesian coordinates appearing in the multidimensional coordinate $\eta_1(\mathbf{r}^N), \ldots, \eta_L(\mathbf{r}^N)$, that, therefore, can be independently constrained, and, more recently, by Coluzza *et al.* [30] in the most general case. The derivations are essentially the same, although much more cumbersome, as the one outlined here with the key point that the conditional averages are now expressed in terms of averages over a molecular dynamics constrained trajectory

$$O_{\text{cond}} = \frac{\langle |\Xi|^{-\frac{1}{2}} \hat{O}(\mathbf{r}^N, \mathbf{p}^N) \rangle_{\eta_1', \ldots, \eta_L'}}{\langle |\Xi|^{-\frac{1}{2}} \rangle_{\eta_1', \ldots, \eta_L'}} \quad (30)$$

in which the role of the factor Z is now taken by the determinant of the $L \times L$ matrix Ξ

$$\Xi_{\alpha\beta} = \sum_i \frac{1}{m_i} \frac{\partial \eta_\alpha}{\partial \mathbf{r}_i} \cdot \frac{\partial \eta_\beta}{\partial \mathbf{r}_i}$$

An example is given in the paper by Maragliano *et al.* [31] with explicit formulas carried out for the case of the dissociation of protein dimers. Armed with such general vectorial formulation of Blue Moon, one can fully explore the reduced dimensionality space of interest to build up amazing free energy landscapes, but at the expense of a very cumbersome procedure. Indeed, there are accelerated methods that are already available and in use [32,33], based on the idea of Landau's filling potential [34,35], which permit to tackle the problem in exactly the same spirit. An even more promising direction, however, appears to be the one recently being explored of new, smarter and numerically more efficient approaches [36–40], where constraints can play the role of very useful implementation tools, that attempt to find out the "reaction path" without any previous knowledge of the reaction coordinate, whose explicit functional dependence from the coordinates would be no longer needed *a priori*.

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