

## CONSTRAINED REACTION COORDINATE DYNAMICS FOR THE SIMULATION OF RARE EVENTS

E.A. CARTER <sup>a,1</sup>, Giovanni CICCOTTI <sup>a,b,2</sup>, James T. HYNES <sup>a</sup> and Raymond KAPRAL <sup>b</sup>

<sup>a</sup> Department of Chemistry and Biochemistry, University of Colorado, Boulder, CO 80309-0215, USA

<sup>b</sup> Chemical Physics Theory Group, Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 1A1

Received 30 December 1988; in final form 18 February 1989

A computationally efficient molecular dynamics method for estimating the rates of rare events that occur by activated processes is described. The system is constrained at "bottleneck" regions on a general many-body reaction coordinate in order to generate a biased configurational distribution. Suitable reweighting of this biased distribution, along with correct momentum distribution sampling, provides a new ensemble, the constrained-reaction-coordinate-dynamics ensemble, with which to study rare events of this type. Applications to chemical reaction rates are made.

Many dynamical systems spend the overwhelming majority of their time in certain well-defined phase space regions, with transitions between these stable regions typically occurring by infrequent activated events of short duration. Diffusion in solids and chemical reactions are well-known examples.

By simulation it is difficult to determine properties that depend on such rare events. A computationally efficient way to estimate the transition rate is to choose initial system states localized at the hypersurface that separates the stable regions. This idea was introduced to treat gas-phase chemical reactions [1,2] and later applied to condensed-phase rate processes [3-5]. This Letter addresses the question of the computation of activated processes described by a general configurational nonlinear many-body reaction coordinate, and gives a method useful for their molecular dynamics simulation. This new method provides an independent alternative to the commonly applied umbrella sampling techniques [6].

We suppose that the activated process is described by the reaction coordinate  $\xi(\mathbf{r})$ , where  $\mathbf{r} = (\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N)$  represents the  $3N$  Cartesian coordinates of the system composed of  $N$  atoms with masses  $m_i$  ( $i = 1, \dots, N$ ). This could be, e.g., an angle in an isomerization [7], an unstable asymmetric stretch in an atom or charge-transfer reaction [8], or a many-body coordinate involving Coulomb interaction energies in an electron or proton transfer reaction [9]. The study of diffusion in solids also entails the use of many-body reaction coordinates [10].

The quantities of interest are ensemble averages of static or time-dependent dynamical variables containing a delta function that localizes the system initially at a prescribed value of  $\xi(\mathbf{r})$ . We show how such averages can be computed and we apply these general results to produce a computable formula for rate constants.

We wish to calculate the quantity  $\langle O(\mathbf{r}, \mathbf{p}^r) \delta(\xi(\mathbf{r}) - \xi') \rangle$ , where  $O(\mathbf{r}, \mathbf{p}^r)$  is any observable,  $\xi'$  is some numerical value of the reaction coordinate  $\xi(\mathbf{r})$ , and  $\langle \rangle$  is the canonical ensemble average. We make the standard assumption [11,12] that the  $N$  atoms form  $M$  molecules through intramolecular forces and/or  $L$  rigid constraints  $\sigma_i(\mathbf{r}) = 0$  ( $i = 1, \dots, L$ ). In such a circumstance one normally introduces a set of independent generalized coordinates  $\mathbf{q}$  and conjugate momenta  $\mathbf{p}^q$  such that  $\mathbf{r} = \mathbf{r}(\mathbf{q})$ , and the statistical mechanics is formulated in terms of these variables. However, it has been shown [11,12] that one may equivalently carry out statistical mechanical computations in terms of the original Cartesian coordinates. In this circumstance, the probability

<sup>1</sup> Permanent address: Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90024-1569, USA.

<sup>2</sup> Permanent address: Dipartimento di Fisica, Università "La Sapienza", Piazzale A. Moro, 00185 Rome, Italy.

associated with the ensemble of interest in the full coordinate and momentum space is

$$P(\mathbf{r}, \mathbf{p}^r) \delta(\xi(\mathbf{r}) - \xi') d\mathbf{r} d\mathbf{p}^r = Q^{-1} \exp[-\beta H(\mathbf{r}, \mathbf{p}^r) \delta(\xi(\mathbf{r}) - \xi')] \prod_{i=1}^L \delta(\sigma_i) \delta(p_i^\sigma - \phi_i) d\mathbf{r} d\mathbf{p}^r, \quad (1)$$

where  $H(\mathbf{r}, \mathbf{p}^r) = K + V$  is the system Hamiltonian in Cartesian coordinates with  $K$  the kinetic energy, and  $Q$  is the partition function. The canonical variables  $(\mathbf{r}, \mathbf{p}^r)$  are in one to one correspondence with new canonical variables  $(\bar{q}, \xi, \sigma, \mathbf{p}^{\bar{q}}, p^\xi, \mathbf{p}^\sigma)$ , and  $\phi_i$  is a function of the unconstrained coordinates  $(\bar{q}, \xi)$  and their associated momenta  $(\mathbf{p}^{\bar{q}}, p^\xi)$  such that  $\mathbf{p}^\sigma - \phi = Z^{-1} \dot{\sigma}$ . (The last equation is derived in the appendix of ref. [12] and  $Z$  is defined below.)

For our purposes it is convenient to rewrite this probability as

$$P(\mathbf{r}, \mathbf{p}^r) \delta(\xi(\mathbf{r}) - \xi') d\mathbf{r} d\mathbf{p}^r = P(\mathbf{r}) \delta(\xi(\mathbf{r}) - \xi') P(\mathbf{p}^r | \mathbf{r}) d\mathbf{r} d\mathbf{p}^r, \quad (2)$$

where the configurational probability is

$$P(\mathbf{r}) \delta(\xi(\mathbf{r}) - \xi') d\mathbf{r} = Q_c^{-1} |Z|^{1/2} \exp[-\beta V(\mathbf{r})] \delta(\xi(\mathbf{r}) - \xi') \prod_{i=1}^L \delta(\sigma_i) d\mathbf{r} \quad (3)$$

and

$$P(\mathbf{p}^r | \mathbf{r}) d\mathbf{p}^r = |Z|^{-1/2} \exp(-\beta K) \prod_{i=1}^L \delta(p_i^\sigma - \phi_i) d\mathbf{p}^r \quad (4)$$

is the conditional probability density of the momenta given the configuration. The total potential energy is  $V(\mathbf{r})$ , and  $|Z|$  is the determinant of the  $L \times L$  matrix  $Z$  with elements

$$Z_{mn} = \sum_{i=1}^N m_i^{-1} (\partial \sigma_m / \partial r_i) \cdot (\partial \sigma_n / \partial r_i). \quad (5)$$

The factors involving  $|Z|$  in eqs. (3) and (4) arise [11,12] from performing the momentum integration in the ensemble average.  $Q_c$  is the configurational partition function. The meaning of the matrix  $Z$ , which has been discussed by several authors [13], has its origin in the fact that imposing  $\sigma_i(\mathbf{r}) = 0$  for all times also requires that the velocities  $\dot{\sigma}_i(\mathbf{r})$  vanish at all times.

The molecular constraints above were introduced for convenience to correspond to conventional practice [11,12] for describing molecules in simulations; they need not be present. We now introduce the constraint on the reaction coordinate that is fundamental to our method. We construct an ensemble by constraining the reaction coordinate at  $\xi'$  ( $\xi(\mathbf{r}) = \xi'$ ,  $\dot{\xi}(\mathbf{r}, \dot{\mathbf{r}}) = 0$ ), along with the previous  $L$  molecular constraints – we term this the  $\xi$ -constrained ensemble. The probability associated with the  $\xi$ -constrained ensemble can be written as the product of the configurational probability

$$P_{\xi'}(\mathbf{r}) d\mathbf{r} = Q_{\xi'}^{-1} |Z|^{1/2} \exp[-\beta V(\mathbf{r})] \delta(\xi(\mathbf{r}) - \xi') \prod_{i=1}^L \delta(\sigma_i) d\mathbf{r}, \quad (6)$$

and a biased conditional probability for the momenta, which is not needed in the subsequent discussion. In eq. (6)  $|Z|^{1/2}$  arises from performing the momentum integration, and the  $(L+1) \times (L+1)$  matrix  $Z$  has a structure analogous to that of  $Z$  (cf. eq. (5)) but is generated by the set of variables  $(\xi, \sigma)$  instead of  $\sigma$  alone.  $Q_{\xi'}$  is the configurational partition function in this constrained ensemble.

At this stage, we can take the essential step. Recall that what is required is to calculate averages in ensemble (2) in which  $\xi$  is *restricted* to the value  $\xi'$ , but is not *constrained* (which requires the additional condition  $\dot{\xi} = 0$ ). However, we wish to express such averages in terms of the  $\xi$ -constrained ensemble designed to frequently produce rare events. To this end, we now define the following ensemble, using eqs. (4) and (6),

$$P_{\xi', M}(\mathbf{r}, \mathbf{p}^r) d\mathbf{r} d\mathbf{p}^r = P_{\xi'}(\mathbf{r}) P(\mathbf{p}^r | \mathbf{r}) d\mathbf{r} d\mathbf{p}^r. \quad (7)$$

We call this the constrained-reaction-coordinate-dynamics (CRCDD) ensemble <sup>#1</sup>. It is straightforward to sample from the configurational distribution (6). It is also not difficult to sample from the conditional momentum distribution (4). With no molecular constraints it is the product of Maxwell distributions; techniques have also been given [14] for sampling from this distribution when molecular constraints are present.

In the CRCDD ensemble, the conditional momentum distribution is that appropriate to the system when  $\xi$  is restricted but not constrained. In contrast the configurational distribution is that appropriate to the  $\xi$ -constrained simulation and is thus distorted from the desired  $\xi$ -restricted distribution (compare eqs. (3) and (6)). The correction factor required for the CRCDD ensemble to reproduce the proper averages in the restricted ensemble is easily obtained by comparing eqs. (7) and (2), and using the quantity  $D = |Z|/|Z|$ . In this way we find our major result

$$\frac{\langle O(\mathbf{r}, \mathbf{p}^r) \delta(\xi(\mathbf{r}) - \xi') \rangle}{\langle \delta(\xi(\mathbf{r}) - \xi') \rangle} = \frac{\langle D^{-1/2} O(\mathbf{r}, \mathbf{p}^r) \rangle_{\xi', M}}{\langle D^{-1/2} \rangle_{\xi', M}}, \quad (8)$$

where  $\langle \rangle_{\xi', M}$  denotes an average over the CRCDD ensemble. The factor  $D^{-1/2}$  serves to remove the bias generated by the constrained molecular dynamics trajectory. The quantity  $D^{1/2}$  has a clear geometrical interpretation: it is the length, with an inverse mass metric, of the component of the vector  $\partial\xi/\partial\mathbf{r}$  orthogonal to the space spanned by the molecular constraint vectors  $\partial\sigma_n/\partial\mathbf{r}$ . That is,

$$D = (\partial\xi/\partial\mathbf{r}) \cdot (\mathbf{1} - \mathcal{P}^{(L)}) \cdot (\partial\xi/\partial\mathbf{r}), \quad (9)$$

where the scalar product of two vectors  $\mathbf{a}$  and  $\mathbf{b}$  is given by  $\mathbf{a} \cdot \mathbf{b} = \sum_{i=1}^N m_i^{-1} a_i b_i$ , and

$$\mathcal{P}^{(L)} = \sum_{m,n=1}^L (\partial\sigma_m/\partial\mathbf{r})(Z^{-1})_{mn}(\partial\sigma_n/\partial\mathbf{r}), \quad (10)$$

is the projector onto the subspace of molecular constraints. This result follows from a straightforward expansion of  $|Z|$  about the elements of the first row.

In eq. (8) the quantity  $\langle \delta(\xi(\mathbf{r}) - \xi') \rangle = P(\xi')$  appears, where  $P(\xi')$  is the probability density of  $\xi'$ . This is indirectly obtained from the CRCDD ensemble, by first calculating its logarithmic derivative in this ensemble and then integrating. To this end, we define the reversible work or mean potential  $W(\xi')$  associated with the reaction coordinate by

$$W(\xi') = -\beta^{-1} \ln[P(\xi')/P_u], \quad (11)$$

where  $P_u$  is the uniform density of  $\xi'$ . The mean force  $F(\xi')$  defined by

$$F(\xi') = -dW(\xi')/d\xi', \quad (12)$$

is easily obtained by introducing the coordinate transformation  $\mathbf{r} \leftrightarrow (\bar{q}, \xi, \sigma) = \mathbf{u}$ , where  $\mathbf{q}$  is a convenient set of generalized coordinates. We find

$$F(\xi') = \frac{\langle (\partial\mathbf{r}/\partial\xi) \cdot [-\partial V/\partial\mathbf{r} + \beta^{-1} \partial \ln(|J| |Z|^{1/2})/\partial\mathbf{r}] \delta(\xi(\mathbf{r}) - \xi') \rangle}{\langle \delta(\xi(\mathbf{r}) - \xi') \rangle}, \quad (13)$$

where  $|J|$  is the Jacobian determinant  $|J| = |\partial\mathbf{r}/\partial\mathbf{u}|$ . A direct application of eq. (8) can be used to calculate  $F(\xi')$  in the CRCDD ensemble. The probability density  $P(\xi')$  can then be obtained by integration of this force.

A few general comments about this result can be made. The average force is obtained from the average of a microscopic variable consisting of two terms: the first is simply the generalized force on  $\xi$ ,  $-\partial V/\partial\xi$ , while the second represents the apparent force that arises from the non-inertial (centrifugal, etc.) character of the

<sup>#1</sup> Since the CRCDD ensemble refers to rare events which occur "once in a blue moon", we feel that an appropriate alternate title would be "blue moon ensemble".

$\xi$  variable. Eqs. (8) and (13) considerably simplify in the special case where the reaction coordinate is the magnitude of the internuclear separation between two particles. An example is the association reaction between two ions in a polar solvent consisting of  $N$  rigid diatomic molecules [15]. The reaction coordinate constraint has the form  $\xi(r_+, r_-) = |r_+ - r_-| - \xi^* = 0$ , with  $r_+$  and  $r_-$  the two ion coordinates. A direct calculation of  $D$  gives the constant value  $D = \mu^{-1}$ , where  $\mu$  is the ion pair reduced mass. The apparent force contribution to eq. (13) is also simple to compute and reduces to the known [16] expression  $2/\beta\xi^*$ ; the generalized force term has been directly computed from constrained molecular dynamics [15] and dominates the apparent force for the ion association problem.

The CRCD ensemble also provides a method to compute time correlation functions. What is required is to take an average over an ensemble of initial conditions of dynamical segments evolved by following the complete time evolution after release of the constraint  $\xi$  (cf. fig. 1). Hence, we may write

$$\frac{\langle O(\mathbf{r}, \mathbf{p}^r) \bar{O}(\mathbf{r}(t), \mathbf{p}^r(t)) \delta(\xi(\mathbf{r}) - \xi^*) \rangle}{\langle \delta(\xi(\mathbf{r}) - \xi^*) \rangle} = \frac{\langle D^{-1/2} O(\mathbf{r}, \mathbf{p}^r) \bar{O}(\mathbf{r}(t), \mathbf{p}^r(t)) \rangle_{\xi^*, M}}{\langle D^{-1/2} \rangle_{\xi^*, M}}, \quad (14)$$

where  $\bar{O}(\mathbf{r}, \mathbf{p}^r)$  is another arbitrary phase space function.

This general approach may now be directly applied to the calculation of the rate constant of a chemical reaction. We suppose that the transition state for the reaction lies at  $\xi(\mathbf{r}) = \xi^*$  and define reactants as those system states with  $\xi(\mathbf{r}) > \xi^*$ , so the reactant species observable is the step function  $\theta(\xi(\mathbf{r}) - \xi^*)$ . If this process is activated a time scale separation exists between the chemical relaxation process and other internal degrees of freedom of the system, and the rate constant is given by the plateau value of  $k(t)$  defined by [4,17]

$$k(t) = \langle \dot{\xi} \delta(\xi(\mathbf{r}) - \xi^*) \theta(\xi(\mathbf{r}(t)) - \xi^*) \rangle / \langle \theta(\xi(\mathbf{r}) - \xi^*) \rangle. \quad (15)$$

The  $t \rightarrow 0^+$  limit of  $k(t)$  is the transition state theory rate constant [4,18]

$$k^{\text{TST}} = \lim_{t \rightarrow 0^+} k(t) = \langle \dot{\xi} \theta(\xi) \delta(\xi(\mathbf{r}) - \xi^*) \rangle / \langle \theta(\xi(\mathbf{r}) - \xi^*) \rangle, \quad (16)$$

which assumes that there is no recrossing of the transition state surface before product is formed. The time-dependent transmission coefficient  $\kappa(t)$  is defined as the ratio  $\kappa(t) = k(t)/k^{\text{TST}}$ , and measures the deviation from  $k^{\text{TST}}$  arising from any recrossings.

In the general case positions and velocities are not independent and the expectation value in eq. (16) does not factor. Carrying out the integration over momenta using  $\dot{\xi} = (\partial\xi/\partial\mathbf{r}) \cdot (\mathbf{p}^r/m)$ , one finds

$$k^{\text{TST}} = (2\pi\beta)^{-1/2} \langle D^{1/2} \delta(\xi(\mathbf{r}) - \xi^*) \rangle / \langle \theta(\xi(\mathbf{r}) - \xi^*) \rangle, \quad (17)$$

which provides an interesting relation for  $k^{\text{TST}}$  as the expectation value of the length of the orthogonal com-

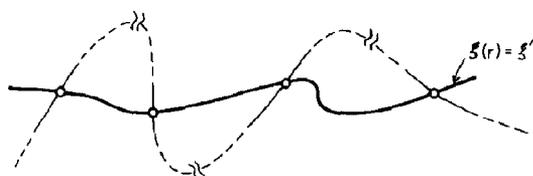


Fig. 1. Schematic representation of the sampling method. The bold line represents the dynamical evolution in phase space with the constraint  $\xi(\mathbf{r}) = \xi^*$ , while the broken light line represents the natural evolution of the system. The crossing points of the two trajectories (open circles) are the initial conditions of our sampling (see text). Note that they do not represent real crossings since these points correspond to identical states in configuration space but different momentum states. The interruptions of the broken light line indicate that the "crossings" of the two trajectories are very rare events. The initial configurations selected by this procedure (open circles) must be weighted by the factor  $D^{-1/2}$  to obtain the correct sampling (see eq. (14)). The dynamics represented by the light line in the vicinity of the crossing points gives the correct dynamical information needed to apply eq. (14).

ponent of the vector  $\partial\tilde{\xi}/\partial r$  introduced earlier (cf. eq. (9)).

We now turn to the computation of these quantities in the CRCD ensemble. A direct application of eq. (8) yields for  $k^{\text{TST}}$

$$k^{\text{TST}} = (2\pi\beta)^{-1/2} \langle D^{-1/2} \rangle_{\xi^*, M}^{-1} P_R(\xi^*), \quad (18)$$

where  $P_R(\xi^*)$  is the probability of being at  $\xi^*$ , normalized by the reactant density  $\langle \theta(\xi(r) - \xi^*) \rangle$ . Eq. (18) has the standard form ( $k^{\text{TST}} = (2\pi\beta\mu_{\text{eff}})^{-1/2} P_R(\xi^*)$ ) but with  $\langle D^{-1/2} \rangle_{\xi^*, M}$  playing the role of the square root of the reaction coordinate effective mass.

Similarly eq. (14), together with eqs. (15) and (16), may be used to compute the transmission coefficient as

$$\kappa(t) = k(t)/k^{\text{TST}} = \langle D^{-1/2} \dot{\xi} \theta(\xi(r(t)) - \xi^*) \rangle_{\xi^*, M} / \langle D^{-1/2} \dot{\xi} \theta(\xi) \rangle_{\xi^*, M}. \quad (19)$$

These results place the general problem of the calculation of the rates of rare events on a firm footing. In the CRCD ensemble generated in the simulation the "rare" events are no longer rare and the time scale of the relevant dynamics is short. (For suitably low barrier reactions, direct simulation methods can be applied to study reactions without selecting transition-state initial conditions [19].) Moreover, a complete, computationally efficient algorithm for the rate constant has been given, regardless of the nature of the configurational reaction coordinate. In this context it is now possible to address questions such as the molecular dynamics simulation of the electron transfer problem which involves a complex highly nonlinear full many-body reaction coordinate [9].

This work was supported in part by EEC contract No. ST2J-0094 (GC), the National Science Foundation US, Grants CHE84-19830 and CHE88-07852 (JTH), the Natural Sciences and Engineering Research Council of Canada (RK), the donors of the Petroleum Research Fund administered by the American Chemical Society (RK, JTH) and a NATO International Collaborative Grant. We thank M. Ferrario for useful discussions.

## References

- [1] J. Keck, *Discussions Faraday Soc.* 33 (1962) 173; *Advan. Chem. Phys.* 13 (1967) 85.
- [2] J.B. Anderson, *J. Chem. Phys.* 58 (1973) 4684.
- [3] C.H. Bennett, in: *Algorithms for chemical computation*, ACS Symp. Ser. No. 46, ed. R.E. Christofferson (Am. Chem. Soc., Washington, 1977).
- [4] D. Chandler, *J. Chem. Phys.* 68 (1978) 2959.
- [5] B.J. Berne, in: *Multiple time scales*, eds. J.U. Brackbill and B.J. Cohen (Academic Press, New York, 1985).
- [6] G.M. Torrie and J.P. Valleau, *J. Comput. Phys.* 23 (1977) 187.
- [7] R.O. Rosenberg, B.J. Berne and D. Chandler, *Chem. Phys. Letters* 75 (1980) 162.
- [8] J.P. Bergsma, B.J. Gertner, K.R. Wilson and J.T. Hynes, *J. Chem. Phys.* 86 (1987) 1356; J.P. Bergsma, J.R. Reimers, K.R. Wilson and J.T. Hynes, *J. Chem. Phys.* 85 (1986) 5625.
- [9] A. Warshel, *J. Phys. Chem.* 86 (1982) 2218.
- [10] C.H. Bennett, in: *Diffusion in solids*, eds. A.S. Nowick and J.J. Burton (Academic Press, New York, 1975); E.H. Rezayi and H. Suhl, *Phys. Rev. Letters* 45 (1980) 1115; *Phys. Rev. B* 25 (1982) 2324; K.D. Becker and C. Hoheisel, *J. Chem. Phys.* 77 (1982) 5108.
- [11] G. Ciccotti and J.-P. Ryckaert, *Computer Phys. Rept.* 4 (1986) 345.
- [12] J.-P. Ryckaert and G. Ciccotti, *J. Chem. Phys.* 78 (1983) 7368.
- [13] M. Fixman, *Proc. Natl. Acad. Sci. US* 71 (1974) 3050; N.G. van Kampen and J.J. Lodder, *Am. J. Phys.* 52 (1984) 419; D. Chandler and B.J. Berne, *J. Chem. Phys.* 71 (1979) 5386.
- [14] J.-P. Ryckaert and G. Ciccotti, *Mol. Phys.* 58 (1986) 1125.

- [15] G. Ciccotti, M. Ferrario, J.T. Hynes and R. Kapral, *Chem. Phys.* 129 (1989) 241.
- [16] M. Sceats, *Advan. Chem. Phys.* 70 (1988) 357.
- [17] T. Yamamoto, *J. Chem. Phys.* 33 (1960) 281;  
R. Kapral, *Advan. Chem. Phys.* 48 (1981) 71;  
J.T. Hynes, in: *The theory of chemical reaction dynamics*, Vol. 4, ed. M. Baer (CRC Press, Boca Raton, 1985).
- [18] R.A. Rosenstein, *Ber. Bunsenges. Physik. Chem.* 77 (1973) 493.
- [19] S.-B. Zhu, J. Lee and G.W. Robinson, *J. Phys. Chem.* 92 (1988) 2401.