

Coordination numbers as reaction coordinates in constrained molecular dynamics

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Reaction coordinates for chemical reactions in solution are often of a collective nature involving solvent degrees of freedom. A recent generalization of the blue-moon ensemble technique has enabled us to determine the free energy required to change these variables, using them as constraints in a molecular dynamics simulation. We discuss a first application to the free energy of coordination fluctuations of an argon atom in liquid argon.

1 Introduction

The development of density functional theory-based *ab initio* molecular dynamics (MD) methods (Car–Parrinello) has advanced to a stage where we can begin to apply this technique in numerical simulation studies of chemical reactions in solution. The results for the comparatively simple systems studied so far are very encouraging, convincing us that this approach can indeed be used to investigate the atomistic detail of chemical processes in a condensed-phase environment, which not only plays the role of a solvent but also actively participates in the reactions as a reactant or catalyst.^{1,2} These features will be crucial for the understanding of complex catalytic reaction mechanisms such as exhibited by enzymes. However, the first applications of *ab initio* MD have also raised a number of issues that must be resolved before this approach can be employed to tackle these more complex reactions. The accuracy of the energetics of reactant, product and transition states as obtained by density functional theory (DFT) is, and will also in the foreseeable future continue to be, one of the most important problems. Another urgent issue is the identification of transition states and the determination of the corresponding free energy of activation.

The search for the location of a transition state, and the reaction path leading to it, has been a much debated problem in the context of the study of gas-phase reactions. Several sophisticated techniques have been developed, such as eigen vector following methods which converge to saddle points in the energy landscape.^{3,4} Extension of these techniques to solution chemistry is not straightforward, because of the interference of dynamical fluctuations in finite-temperature condensed phases. These fluctuations cannot be ignored because they form the basis for the entropic component of activation energies in solution. In fact, quenching of the finite-temperature dynamics, as occurs in most of these gas-phase optimization techniques, would lead to freezing of the solvent and loss of many of its solvation properties which depend on the liquid state. Hence, for application in solution chemistry, a new generation of statistical search techniques is required such as, for example, the path integral methods discussed in the contribution by the group of David Chandler.

When some information about the reaction mechanism is available, either from experiment or as a theoretical hypothesis, we can attempt to define an approximate

reaction coordinate ξ describing this process. ξ is an analytical function $\xi(\mathbf{r}^N)$ of the cartesian coordinates $\mathbf{r}^N = \mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N$ of the N particles (atoms) in our model system. This predefined reaction coordinate can then be used as the control parameter in techniques for the simulation of rare events, such as umbrella sampling⁵ or constraint methods.^{6–8} This enables us to explore the reaction path, determine quantitative characteristics such as relative free energies and reaction rates and compare with similar data obtained for alternative reaction mechanisms. The method of constraints is, by construction, adapted to MD implementation and has been used in most of the *ab initio* MD studies of chemical reactions.^{1,2}

The application of the method of constraints has been limited to simple geometric reaction coordinates, such as distances and dihedral angles. However, the reaction coordinates relevant in solution chemistry often involve many degrees of freedom, including reactants as well as solvent molecules. An elementary example is the calculation of the pK_a of a weak acid HA in aqueous solution. Unlike the case of a strong acid, the free energy of dissociation cannot be obtained by removing the H^+ from its conjugate base A^- by a stepwise increase of the constrained distance between these two ions. Before the extraction has been completed, a proton supplied by the surrounding solvent will have replaced it, resulting in a proton exchange instead of dissociation. Certain technical difficulties have effectively prevented the use of constraints to investigate collective processes such as this, even though these reactions are typical of condensed-phase chemistry and catalysis.

The complications that are responsible for frustrating the extension of the method of constraints to more complex reaction coordinates become already apparent when we recall the thermodynamic integration scheme underlying the evaluation of free energy in this method. This fundamental concept in statistical mechanics relates the difference in free energy $W(\xi)$ between states characterized by reaction coordinate values $\xi = \xi_1$ and $\xi = \xi_2$ to the reversible work needed to change the state of the system along a path connecting these two states.

$$W(\xi_2) - W(\xi_1) = \int_{\xi_1}^{\xi_2} d\xi' \left\langle \frac{\partial \mathcal{H}}{\partial \xi} \right\rangle_{\xi'}^{\text{cond.}} \quad (1)$$

\mathcal{H} is the Hamiltonian of our system. The free energy for a given value $\xi = \xi'$ on the left-hand side of eqn. (1) can be given a direct probabilistic interpretation

$$W(\xi') = -kT \ln P_{\xi}(\xi') \quad (2)$$

where the probability distribution P_{ξ} is an equilibrium quantity obtained by

$$P_{\xi}(\xi') = \langle \delta[\xi(\mathbf{r}^N) - \xi'] \rangle \quad (3)$$

Whereas the brackets in eqn. (3) denote a standard average over the canonical ensemble, the average of the generalized force $\partial \mathcal{H} / \partial \xi$ in eqn. (1) is restricted to the subset of states with $\xi(\mathbf{r}^N) = \xi'$. This conditional average can be expressed in terms of regular canonical averages as

$$\langle \mathcal{O}(\mathbf{r}^N, \mathbf{p}^N) \rangle_{\xi'}^{\text{cond.}} = \frac{\langle \mathcal{O}(\mathbf{r}^N, \mathbf{p}^N) \delta[\xi(\mathbf{r}^N) - \xi'] \rangle}{\langle \delta[\xi(\mathbf{r}^N) - \xi'] \rangle} \quad (4)$$

where $\mathcal{O}(\mathbf{r}^N, \mathbf{p}^N)$ is a general phase function. It is this condition on the ensemble that enables us to sample the mean force for values of ξ with low probability, such as a transition state, by imposing the corresponding constraint $\xi(\mathbf{r}^N) = \xi'$ on the system.

Eqn. (1) closely resembles the thermodynamic integration formula for free energy changes corresponding to variation of coupling parameters in the Hamiltonian. However, a reaction coordinate is not an independent parameter but a function of the

configurational degrees of freedom \mathbf{r}^N . This distinction has a number of implications. First is the correlation of free energy to a probability distribution as expressed in eqn. (2) and (3). A second, more unpleasant, consequence is that the dependence of the Hamiltonian on ξ is not explicit which makes it difficult to perform the partial derivative with respect to ξ required to determine the generalized force in eqn. (1). In fact, for most of the collective reaction coordinates of interest in solution chemistry the relation of eqn. (1) cannot be employed without transformation to a more convenient form.

A way out of this problem is using the force of constraint as a substitute for the generalized force $\partial\mathcal{H}/\partial\xi$. This quantity is automatically provided by the numerical solution of the constrained equations of motion in the form of a Lagrange undetermined multiplier. This approach has been recently proposed by Mülders *et al.*⁹ The rationale is that the force of constraint must compensate the total generalized force $\partial\mathcal{H}/\partial\xi$ including the inertial force term $\partial\mathcal{K}/\partial\xi$. Writing the Hamiltonian equation of motion for ξ

$$\dot{p}^\xi = -\frac{\partial\mathcal{H}}{\partial\xi} - \lambda \quad (5)$$

where \dot{p}^ξ is the generalized momentum conjugate to ξ , even leads us to the conclusion that the corresponding Lagrange multiplier λ is identical to the total force and, hence, contains all the information we need. While appealing to mechanical intuition, a rigorous justification, however, is not straightforward. In fact the derivation given in ref. 9 is not correct, ignoring a further level of complication related to the dynamical nature of reaction coordinates. Proper account of these effects gives rise to corrections which are less intuitively clear. These corrections follow from an extension of the so-called blue moon ensemble technique introduced by Ciccotti and co-workers⁶ and will be derived in a forthcoming publication.¹⁰ In this contribution, after a short summary in the next section, we will discuss an application to a simple example of a collective reaction coordinate, namely the number of nearest neighbours of a single selected argon atom in liquid argon. Our aim is to get a better feeling for the behaviour of these corrections and to assess their importance in a problem representative of conditions encountered in the study of chemical reactions in solution.

2 Summary of methodology

Along an MD trajectory in which the reaction coordinate ξ is held fixed by a constraint $\xi(\mathbf{r}^N) = \xi'$, not only is the observable ξ constant but also its time derivative $\dot{\xi} = 0$. The additional constraint on velocity, which is absent from the conditional average of eqn. (4), introduces restrictions in the sampling of momenta. When not unbiased, this violation of equipartition in cartesian momentum space can lead to real discrepancies between an average over a constrained trajectory and the conditional average of eqn. (4). These inconsistencies occur not only for momentum-dependent phase functions $\mathcal{O}(\mathbf{r}^N, \mathbf{p}^N)$ but also for purely configurational functions $\mathcal{O}(\mathbf{r}^N)$ (for an example see the text book of Frenkel and Smit⁸). In the context of the calculation of mean force and free energy for reaction coordinates, this somewhat paradoxical effect can be considered as yet another consequence of reaction coordinates being dynamical variables rather than parameters.

The remedy for the determination of averages of configurational functions has been worked out some time ago,¹¹ and consists of a reweighting scheme for the points on the constrained trajectory

$$\langle \mathcal{O}(\mathbf{r}^N) \rangle_{\xi'}^{\text{cond.}} = \frac{\langle Z^{-1/2} \mathcal{O}(\mathbf{r}^N) \rangle_{\xi'}}{\langle Z^{-1/2} \rangle_{\xi'}} \quad (6)$$

where the subscript ξ' indicates that the brackets are an average over the ensemble generated by the constrained dynamics. The factor Z is defined by

$$Z = \sum_i \frac{1}{m_i} \left(\frac{\partial \xi}{\partial \mathbf{r}_i} \right)^2 \quad (7)$$

The unbiased constrained ensemble is usually referred to as a blue-moon ensemble. Unfortunately, the relation of eqn. (6) cannot be applied to the conditionally averaged generalized force in the right-hand side of eqn. (1) because this quantity depends on momenta through the contribution of the kinetic term.

This dilemma was resolved by Ciccotti *et al.* in ref. 6 by reducing the generalized force $\partial \mathcal{H} / \partial \xi$ to a configurational function by performing the conditional integral over momentum space. The result is the blue-moon expression for mean force, as it has been employed in most applications of the method of constraints

$$\frac{dW}{d\xi'} = \frac{\left\langle Z^{-1/2} \left[\frac{\partial \mathcal{V}}{\partial \xi} - kT \frac{\partial \ln |J|}{\partial \xi} \right] \right\rangle_{\xi'}}{\langle Z^{-1/2} \rangle_{\xi'}} \quad (8)$$

The term with the logarithmic derivative added to the potential force $\partial \mathcal{V} / \partial \xi$ is the temperature-dependent contribution of the inertial forces. It depends on the determinant of the Jacobian matrix J of a transformation from the cartesian representation to a set of coordinates which includes the reaction coordinate ξ .

While eqn. (8) provides us with an unbiased procedure for estimating mean force from constrained MD trajectories, it is not very practical because it still involves the partial derivatives with respect to ξ . As explained in the Introduction, this is the operation we would like to avoid. Moreover, the suspicion that this inconvenience is caused by our choice of representation is even strengthened by the appearance of the Jacobian in eqn. 8, which is not only a function of ξ but also of the complementary coordinates perpendicular to ξ . Clearly, the mean force cannot depend on this level of detail. Using the Lagrange multiplier λ as a measure for the total force, as suggested by eqn. (5), would indeed relieve us of this problem, because this quantity can be computed in the cartesian representation without the need for transformation to generalized coordinates. This is evident from the familiar formal expression for the Lagrange multiplier obtained by substitution by Newton's equations of motion in the second time derivative of the constraint relation $\xi(\mathbf{r}^N) = \xi'$. Using the summation convention for multiple particle indices i, j, k we can write

$$\lambda = Z^{-1} \left[\dot{\mathbf{r}}_j \frac{\partial^2 \xi}{\partial \mathbf{r}_j \partial \mathbf{r}_k} \dot{\mathbf{r}}_k - \frac{1}{m_i} \frac{\partial \mathcal{V}}{\partial \mathbf{r}_i} \frac{\partial \xi}{\partial \mathbf{r}_i} \right] \quad (9)$$

where \mathcal{V} is the N particle potential function. Unfortunately, we are not allowed to use the procedure of eqn. (6) to convert a constrained average of λ to the conditional average required in eqn. (1) because λ is not a pure configurational function but is also dependent on velocity, as is clear from eqn. (9). The solution of this problem will be presented

in detail in ref. 10. The route we follow there essentially amounts to evaluation of the unbiased (blue-moon) average [eqn. (6)] of the right-hand side of eqn. (9), and comparing the result with eqn. (8) to find out what we are missing to obtain the complete mean force. The difference is, in fact, not zero and can be written as a correction term depending on the curvature of the hypersurfaces of constant ξ . Our final expression for the mean force is

$$\frac{dW}{d\xi'} = \frac{\langle Z^{-1/2} [-\lambda + kT\rho] \rangle_{\xi'}}{\langle Z^{-1/2} \rangle_{\xi'}} \quad (10)$$

with the quantity ρ defined as

$$\rho = \frac{1}{Z^2} \sum_{i,j} \frac{1}{m_i m_j} \frac{\partial \xi}{\partial \mathbf{r}_i} \frac{\partial^2 \xi}{\partial \mathbf{r}_i \partial \mathbf{r}_j} \frac{\partial \xi}{\partial \mathbf{r}_j} \quad (11)$$

The expression of ρ again contains exclusively explicit derivatives with respect to cartesian coordinates, which can be easily computed.

3 Application to coordination number

A relatively simple collective reaction coordinate, which is relevant for the simulation of chemical reactions in solution, is coordination number. An analytic configuration function $\xi(\mathbf{r}^N)$, suitable for imposing a holonomic constraint on the coordination number of a specific atom labelled by index $i = 0$, can be constructed by introducing weights S in the standard procedure for determining the instantaneous radial distribution with particle $i = 0$ as reference. This gives a coordination number reaction coordinate function of the form

$$n_0(\mathbf{r}^N) = \sum_{i>0} S(|\mathbf{r}_i - \mathbf{r}_0|) \quad (12)$$

Atoms $i \neq 0$ within a distance $r < r_c$ with respect to $i = 0$ are assigned weight $S = 1$ whereas atoms with $r > r_c$ have weight $S = 0$. In order to obtain an analytic function we have to allow for a transition region $r \approx r_c$ of intermediate weight $0 < S < 1$. A convolution $S(r)$ of the radial distribution of this type is the Fermi function defined by

$$S(r) = \frac{1}{\exp[\kappa(r - r_c)] + 1} \quad (13)$$

where κ^{-1} is the width of the transition region. In order to be effective as a constraint on coordination, κ^{-1} must be significantly smaller than the coordination radius r_c . The forces \mathbf{g}_i exerted by this constraint function on the atoms $i \neq 0$ are directed along the radius vector with origin \mathbf{r}_0 with a strength proportional to the Lagrange multiplier λ . We have

$$\mathbf{g}_i = -\lambda \frac{\partial n_0}{\partial \mathbf{r}_i} = \frac{1}{2} \frac{\lambda \kappa}{\cosh[\kappa(r_{i0} - r_c)] + 1} \frac{\mathbf{r}_{i0}}{r_{i0}} \quad (14)$$

with $\mathbf{r}_{i0} = \mathbf{r}_i - \mathbf{r}_0$. As can be seen from eqn. (14), the constraint forces only act on the particles in the narrow shell around $r = r_c$. Depending on the sign of λ , the particles passing through this region are either pulled into the coordination sphere ($\lambda < 0$) or removed from it ($\lambda > 0$). The central particle, $i = 0$, is subjected to the combined reaction force $-\sum_{i>0} \mathbf{g}_i$. Note that, for well defined coordination spheres with a sharp truncation at r_c (*i.e.* $\kappa^{-1} \ll r_c$), the constraint forces assume the character of impulse forces with diverging magnitude. It will be clear that this sets an upper limit to κ in an MD scheme.

The system we selected for a first test is liquid argon at a temperature of 150 K. This system is, of course, rather different from the aggressive solvents such as water we have in mind for eventual applications. Liquid argon is, however, convenient for the purpose of a critical examination of the behaviour of the quantities of interest, λ , Z and ρ , in various limits, since it enables us to minimize the inevitable statistical uncertainties under extreme conditions (*e.g.* small width κ^{-1}). A system of 256 atoms was used in a cubic box with length $L = 25 \text{ \AA}$. This yields, at $T = 150 \text{ K}$ for the usual 12-6 interaction ($\epsilon = 120 \text{ k}$, $\sigma = 3.4 \text{ \AA}$) a pressure of *ca.* 250 bar. The simulations were performed under conditions of constant volume and energy with occasional temperature scaling. The coordination of only a single particle of the total of 256 was controlled.

Fig. 1 shows the function $S(r)$ of eqn. (13) for the parameters $r_c = 5.5 \text{ \AA}$ and $\kappa^{-1} = 0.2 \text{ \AA}$ superimposed on the equilibrium radial distribution. This value of r_c sets the truncation of coordination number approximately at the minimum in the pair correlation. With the uncertainty $\kappa^{-1} = 0.2 \text{ \AA}$ the equilibrium (unconstrained) value for the coordination is $\langle n_0(r^N) \rangle = 11.1$, which is a little lower than the average coordination of 11.4 obtained from integration of the radial distribution truncated at a radius of 5.5 \AA . This small discrepancy can be attributed to the fact that the $S(r)$ function is only an approximation to an ideal step function (see Fig. 1). This function was used in a series of runs constrained at integer values for the coordination centred at particle $i = 0$. The constraint varied from $n_0 = 9$ to 15. The resulting blue-moon estimate of mean force [eqn. (10)] and its integral is shown in Fig. 2. The mean force is zero at $n_0 = 11.2$. This is in good agreement with the unconstrained equilibrium expectation value of $\langle n_0 \rangle = 11.1$.

The mean force in Fig. 2 is, to a very good approximation, determined by the $-\lambda$ term in eqn. (10) (see below). Therefore, the coordination number dependence of mean

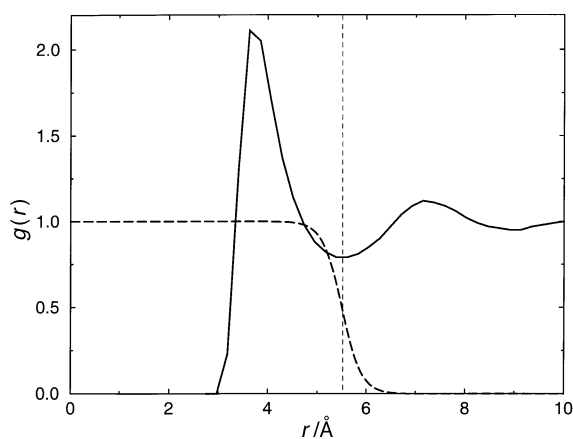


Fig. 1 Fermi function $S(r)$ of eqn. (13) used to define a constraint for coordination (----) superimposed on the radial distribution of liquid argon at $T = 150 \text{ K}$ (—). The value of the parameters in the function are for the cut-off (coordination) radius $r_c = 5.5 \text{ \AA}$ (indicated by vertical line) and for the uncertainty (smoothing) $\kappa^{-1} = 0.2 \text{ \AA}$.

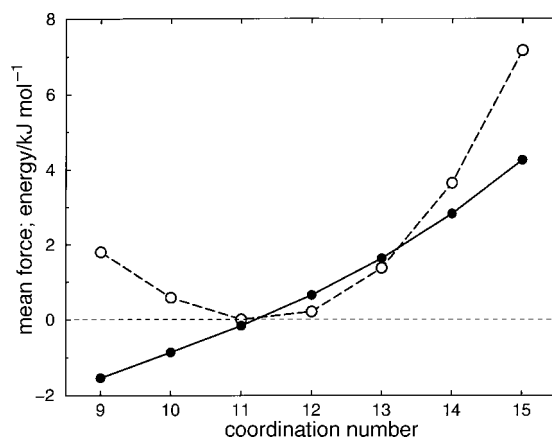


Fig. 2 Mean force (—) as a function of constrained coordination number. (----) Integral with the free energy set to zero at the mean force equilibrium point.

force in Fig. 2 can be interpreted in terms of the action of forces of constraint. The negative λ for overcoordination ($n_0 > 11.2$) implies, on average attractive forces of constraint, and increase in free energy when more atoms are forced inside the coordination sphere. λ changes sign for undercoordination ($n_0 < 11.2$), which indicates a predominance of repulsive constraint forces and, hence, increase of free energy when the coordination sphere is further depleted. Integrating the mean force in Fig. 2, we find that an increase in coordination by 3 with respect to the equilibrium value requires 7 kJ mol^{-1} . A reduction of coordination by the same amount, on the other hand, costs considerably less free energy, namely 2 kJ mol^{-1} , confirming our expectation that the free energy profile for coordination fluctuations is asymmetric.

Fig. 3 gives an impression of the importance of the corrections introduced by the blue-moon ensemble treatment. According to eqn. (10) we can distinguish two contributions which are not taken into account when the mean force is obtained from a straight average of λ over a constrained trajectory. First, there is the effect of multiplication of the Lagrange multiplier by the $Z^{-1/2}$ weight factors and second, the presence of an additional term, $kT\rho$. Comparing the data in Fig. 2 and 3, we see that the correction for each of these effects is at most 10%. This is a modest but not insignificant number. However, because of the opposite sign with which λ and $kT\rho$ enter in the expression for the final mean force [eqn. (10)] the corrections cancel out. The conclusion is that, for the coordination number constraint defined by the Fermi function of Fig. 1, the bare Lagrange multiplier is indeed a very good approximation to the mean force.

Of more interest in this respect is the effect of sharpening of the cut-off, *i.e.* a reduction of the width κ^{-1} . This is shown in Fig. 4 for the $n_0 = 12$ constraint. When the width is increased, the force of constraint and $kT\rho$ must ultimately vanish. The reason is that the Fermi function becomes less discriminative, approaching, for very large width, a constant, irrespective of the value of the cut-off. However, the response to a decrease in the width is less predictable. The forces of constraint become stronger with the peak values of λ favoured by the unbiasing procedure. The result is a distinct enhancement of the blue-moon ensemble average of λ . For $\kappa^{-1} = 0.125 \text{ \AA}$ the uncorrected average over the constrained trajectory is a factor of *ca.* two smaller. Similarly the magnitude of the $kT\rho$ term becomes larger, but the increase is less pronounced compared with the effect on λ .

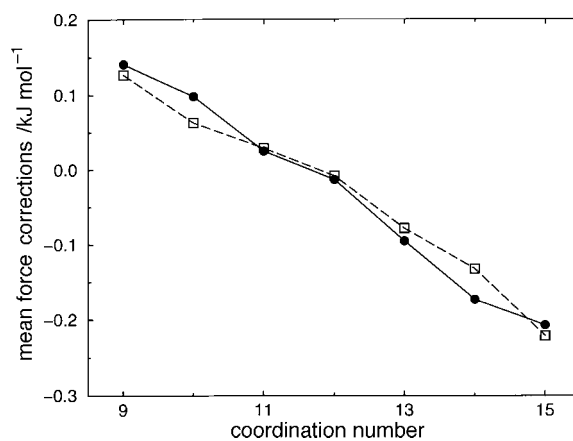


Fig. 3 Corrections included in the mean force of Fig. 2 as a consequence of the use of the blue-moon ensemble technique. (—) Difference of the average of the Lagrange multiplier λ over the constrained trajectory with respect to the average unbiased by blue-moon weights. (----) Blue-moon average of the $kT\rho$ term appearing in eqn. (10).

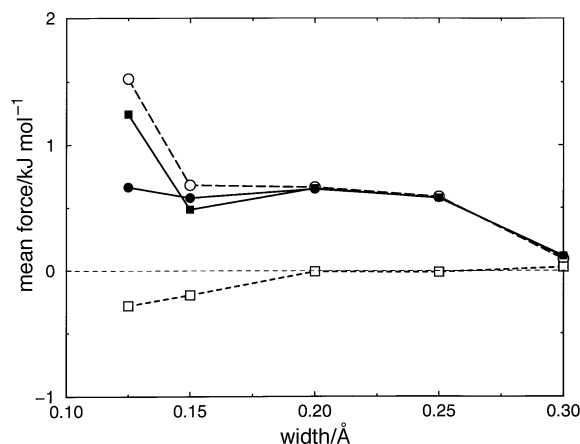


Fig. 4 Contributions to the mean force as a function of the width parameter in the Fermi function determining the precision of the definition of coordination number (see Fig. 1). (●) and (○) Direct constrained and unbiased constrained average of the Lagrange multiplier, respectively; (□) values of $kT\rho$ and (■) result for the full mean force.

For steeper Fermi functions, sampling becomes increasingly more difficult, owing to the increase in the strength of the constraint forces. As explained above, the effect of the constraint on the atoms for very small width is similar to hitting a narrow square-well potential. The consequence is that we are forced to reduce the time step. Unfortunately, this is not the only effect that makes the calculation more expensive in terms of CPU time. In addition to growing more violent, impact of the impulse forces also becomes less frequent. At the same time, the corresponding steep fluctuations in λ are assigned overwhelmingly large weights by the blue-moon factors, which are proportionally enhanced during such an event. This is illustrated in Fig. 5 for $\kappa^{-1} = 0.1 \text{ \AA}$. In fact, the effect is so severe that it was very difficult to collect sufficiently accurate statistics for the $\kappa^{-1} = 0.1 \text{ \AA}$ system, since this requires an excessively long run. For this reason the $\kappa^{-1} = 0.1 \text{ \AA}$ point is omitted from Fig. 4. It will be clear that such sharply defined coordination constraints are not feasible in practice. Neither are they necessary, as is suggested by the plateau in Fig. 4.

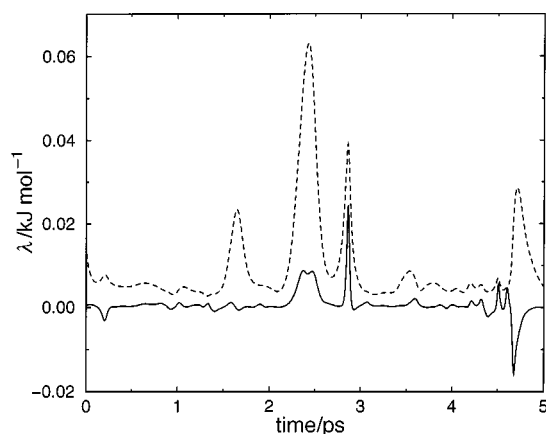


Fig. 5 Time evolution of Lagrange multiplier λ (—) and $Z^{-1/2}$ weight factor (----) (in arbitrary units) for an $n_0 = 12$ constraint with width $\kappa^{-1} = 0.1 \text{ \AA}$

4 Conclusion

The expression of eqn. (10) for the mean force enables us to determine the free energy for variation of configurational properties by using these quantities as constraints in an MD run. There is, in principle, no restriction on the complexity of these variables. An example of interest for simulations of chemical reactions in solution is coordination of reactive solutes. However, this technique can also be used to control complex order parameters in soft condensed matter, such as features of the structure factor, conformation of polymers or defects in liquid crystals and to calculate the free energy required to change these properties. Extrapolating from the experience gathered from the simple application discussed in this contribution, we expect that, in many systems, the Lagrange multiplier will yield a good first approximation to the mean force. We also suggest that the cases for which this is not true can be recognized from distinct, comparatively rare fluctuations in the Lagrange parameter, such as illustrated in Fig. 5, which are an indication that sampling in the blue-moon ensemble is necessary.

I thank Giovanni Ciccotti for his crucial contributions and support. Without his guidance I would have been lost in the pale-blue moonlight of the world of constraints.

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