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Exploring the idea of self-guided dynamics

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We have examined the recently proposed concept of self-guiding in the context of both stochastic and deterministic dynamics of a test particle in a double-well potential. In contrast to the original suggestion, results from our stochastic dynamics simulations indicate that enhancement of the systematic part of the force by introduction of a self-guiding term actually decreases the sampling efficiency of the system. It was found that only by substantially reducing the correlation between the actual force and the self-guiding force an enhancement in sampling could be achieved. In a deterministic analog of the same problem, constructed by coupling the test particle to a bath of a number of harmonic oscillators, an analogous reduction in the barrier crossing rate could be observed for the case when the actual force and the biasing force were strongly correlated. However, even a moderate decorrelation resulted in appreciable enhancement in barrier crossings. For the deterministic dynamics of the test particle uncoupled to the bath, no decrease in sampling was observed. We suggest that depending on the inertial memory of the system, the degree of correlation between the actual and the biasing force determines whether sampling will increase or not. This provides a unified picture and gives us insight about the applicability of the method under different simulation conditions. © *2001 American Institute of Physics.* [DOI: 10.1063/1.1351854]

INTRODUCTION

To have theoretical insight into many molecular processes and phenomena in biophysics, one needs to explore the conformational space of the macromolecules. In spite of rapid advances in computational techniques and hardware, this is still a daunting task considering the dimensionality and complexity of the conformational space of a macromolecule. Methods that in some way or other expedite the search process are therefore much welcome to investigators.

One recent method[1,2] proposed to achieve a substantial speeding up of the search process by selectively influencing the ''systematic part'' of molecular motion. In the framework of molecular dynamics (MD), this was achieved by adding a contribution of the average force from a few previous time steps to the force acting at the present moment. For macromolecules, an additional prescription was suggested to separately enhance ''systematic parts'' of motion from random components of the forces, by defining bonded substructures.[1] The biasing force for an atom in a given substructure, i.e., the average force of some previous steps, came from contributions outside this substructure. The exact contribution and the averaging times were selected empirically. Application of the above method to Lennard-Jones spheres, alanine dipeptide, and a 16-residue synthetic peptide showed a dramatic improvement in conformational search.

Usually, in methods with similar objectives, such as multicanonical MD (Ref. 3) or conformational flooding,[4] one first carries out a preliminary exploration of the conformational space and with the knowledge of the potential energy surface thus gained, biases it suitably either to get enhanced sampling of the less accessible regions or to escape from a local minimum. In contrast, the self-guided MD method, along with the recently proposed method of stochastic scaling of intermolecular interactions,[5] bias the energy surface ''on the fly'' and thus offer definite advantages over other methods.

Stochastic dynamical models in bistable potentials are quite popular for various applications in physical, chemical, and biological systems. In many cases involving the dynamics of a macromolecule, one is actually interested in only a few degrees of freedom in which major movements (''essential dynamics'') are taking place[6] and the dynamics of the rest can be ignored or taken care of in a relatively approximate manner. Consideration of stochastic dynamics thus becomes relevant, because in most cases, the effect of bulk solvent molecules or the effect of the ''scaffolding'' part of the macromolecule on the important degrees of freedom can be seen as a stochastic perturbation and modeled as such. An example of such approximation is a recently proposed model that represents the domain motion in a macromolecule during conformational transitions as a stochastic dynamics in a two-dimensional energy surface where the potential wells were designed to mimic Lennard-Jones or Morse potentials.[7]

In the present study, we have applied the idea of self-guiding to stochastic dynamics in low dimensions to have a better understanding of the functioning of the method. By

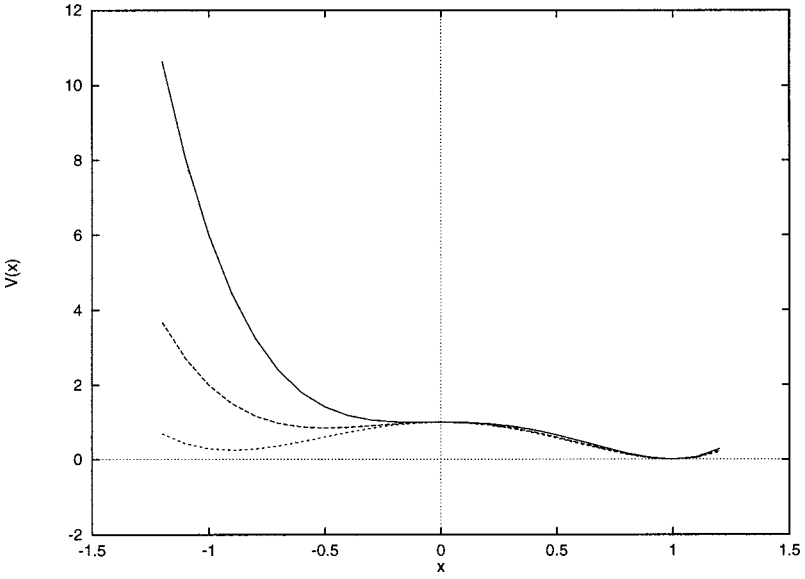

FIG. 1. Double-well potentials in one dimension with $\alpha=0.1$ (solid line), $\alpha=0.5$ (dashed line), and $\alpha=0.9$ (short dashes).

comparing the behavior of our system in the diffusive stochastic dynamics regime with self-guided molecular dynamics simulations, we find that while for stochastic dynamics the rate of barrier crossing decreases with increasing λ (a parameter that modulates the contribution of the biasing force to the dynamics), this behavior can be observed for the case of molecular dynamics only when the correlation between the systematic force and the self-guiding force is very high. For a moderate lack of correlation between the latter two quantities, the barrier crossing rate increases with λ. We argue that this difference in behavior between molecular dynamics and stochastic dynamics may stem from the fact that in the case of stochastic dynamics, the memory of the velocity from the previous step is completely lost.

COMPUTATIONAL DETAILS

We compare the behavior of different dynamical schemes with double-well potentials defined by the quartic polynomial[8]

$$V(x)=3\,\delta x^4+4\,\delta(\alpha-1)x^3-6\,\delta\alpha x^2+1, \tag{1}$$

where

$$\delta=\frac{1}{2\alpha+1}. \tag{2}$$

In Fig. 1, we depict this function for various values of the parameter α within the range $0\leqslant\alpha\leqslant 1$. The function has a fixed minimum (which is also the global minimum) located at $x=1$, a fixed barrier of unit height at $x=1$, and a minimum of variable height located at $x=-\alpha$. One can also recast α in terms of a more physically meaningful parameter by considering the ratio of well depths,

$$\gamma=\frac{V(0)-V(-\alpha)}{V(0)-V(1)}. \tag{3}$$

To make the potential surface more complicated, one can move to a larger number of dimensions

$$V(\mathbf{x})=\sum_{k=1}^{D} V_1(x_k), \tag{4}$$

where $V_1(x_k)$ is the one dimensional double well potential given by Eq. (1) and D is the number of dimensions. The potential hypersurface gets fairly complicated with an increase in the number of dimensions as the number of wells increase as 2^D, of which the global minimum well depth remains unity while the other wells have depths of γ, γ^2, ..., γ^D. Figure 2 shows a plot of the potential energy surface for two dimensions. The global minimum is at (1,1) and the shallowest one is at $(-\alpha,-\alpha)$, while the other two minima have equal depths.

In the self-guided molecular dynamics method proposed by Wu and Wang,[1,2] the authors suggested adding at each step of the dynamics a bias to the actual force obtained from the potential. The biasing force, which the authors call the self-guiding force, is obtained by averaging for a certain length of time t_l the force acting on a particular atom. The contribution of this biasing force to the net force is modulated through the introduction of a parameter λ. In actual practice, the self-guiding force is calculated as[1,2]

$$g_\mu(t)=\left(1-\frac{\Delta t}{t_l}\right)g_\mu(t-\Delta t)+\frac{\Delta t}{t_l}[f_\mu(t)+\lambda g_\mu(t-\Delta t)], \tag{5}$$

where $f_\mu(t)$ is the x,y or the z component of the true force at time t and Δt is the time step. At the beginning, $g_\mu(0)$ is set to 0. λ, the guiding factor, is a parameter that determines the contribution from the guiding force and t_l is the time for averaging the guiding force which is chosen to be greater than the time step Δt. Because of the fictitious guiding force, energy is no longer conserved in a molecular dynamics simulation. To carry out the simulation under the conditions of constant energy or constant temperature, velocities have to be scaled appropriately at each time step.

In our stochastic simulations, we work in the so-called ''diffusive regime.'' The positional updating scheme in this

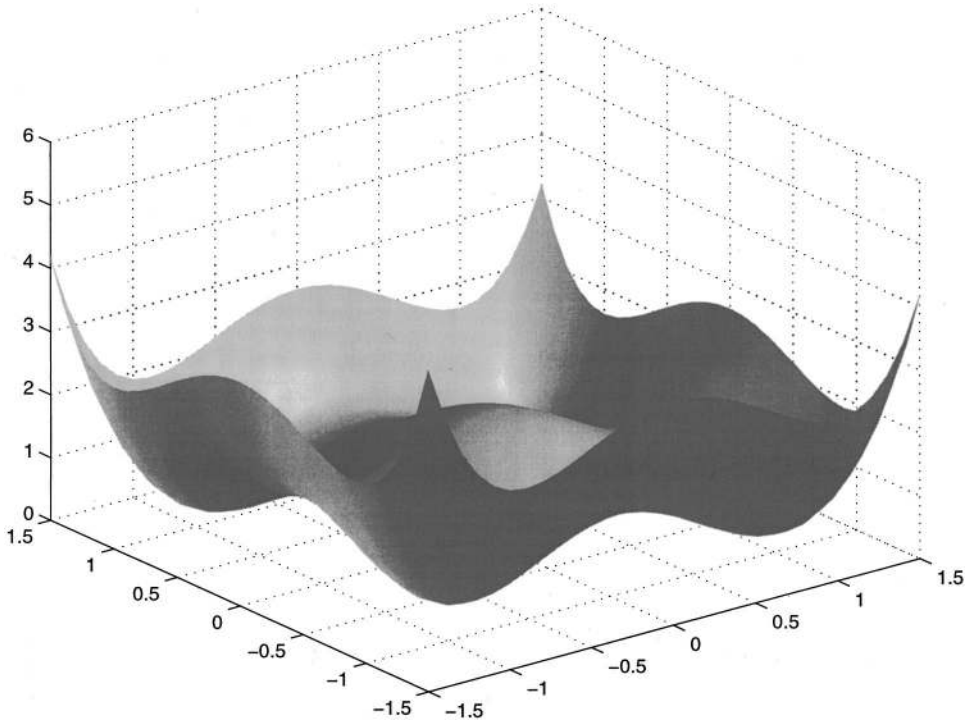

FIG. 2. The potential energy surface in 2D for $\alpha=0.9$.

regime for one Cartesian component μ of a Brownian particle moving in a potential field is given by[9,10]

$$r_\mu(\Delta t)=r_\mu+\frac{h}{T}f_\mu\Delta t+R_\mu, \tag{6}$$

where T is the temperature in energy units, h is the self-diffusion coefficient, Δt is the time step, R_μ is a normally distributed random displacement with zero mean, and

$$\langle R_\mu R_\nu\rangle=2h\Delta t\,\delta_{\mu\nu}. \tag{7}$$

As in the molecular dynamics case, for simulating self-guided motion, we bias the potential derived force (the systematic component) f_μ to $f_\mu+\lambda g_\mu$.

In the stochastic simulations, we used arbitrary units in which the values of h and T were kept at 0.1 (for calculating mean first escape time or number of barrier crossings, the values of h and T were however set to 0.3 to increase the number of transitions between basins). The time step Δt was set to 0.0001. Trajectories were calculated for 10 million time steps saving every 1000th step. In most of the results reported, the simulations were started from the point (0,0). However, different initial points were examined to check whether it has any effect on the general conclusions.

Molecular dynamics simulations were carried out on a chain of $N+1$ oscillators (Fig. 3) in which those numbered 1 to N has on-site harmonic potentials,[11]

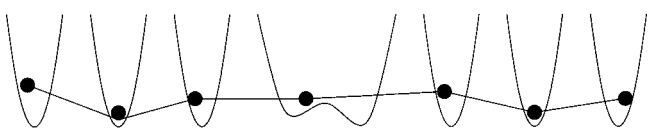

FIG. 3. Diagram of a part of a one-dimensional chain of coupled oscillators interacting with a particle moving in the double-well potential. (Drawn after Fig. 3 of Ref. 11.)

$$H=\sum_{k=1}^{N}\left[\frac{v_k^2}{2}+\frac{c}{2}(x_k-x_{k-1})^2+\frac{1}{2}x_k^2\right], \tag{8}$$

and the particle at the $N+1$th site is subjected to the bistable potential given in equation (1). We assume also the existence of the periodic boundary conditions, so that the oscillators 1 and $N+1$ are coupled together in the same way as the rest of the oscillators in the chain. Molecular dynamics simulations of this deterministic model were carried out with the Verlet leapfrog algorithm.[12]

The self-guiding force at each step was calculated from Eq. (5). However, it was only the systematic part of the force coming from the quartic potential that was used to calculate the self-guiding term. The resulting velocity was scaled by the factor χ_E in one of the half-steps of the leapfrog integrator,

$$v_k'\left(t+\frac{\Delta t}{2}\right)=\chi_E v_k\left(t-\frac{\Delta t}{2}\right), \tag{9}$$

where χ_E is calculated at each step by equating the kinetic energy change with the negative of the potential energy change.[1]

The initial positions were selected as the zeros of the respective coordinates for the molecular dynamics simulations and velocities were drawn from a Maxwellian distribution corresponding to an initial temperature which was taken as 0.5 in arbitrary units for our simulations. The coupling parameter c was also kept at 0.5 for all the simulations. One million time steps of dynamics were investigated for each run with a step length of 0.001 and a saving frequency of 1000 steps.

For analysis of the dynamics we used the mapping function,[11]

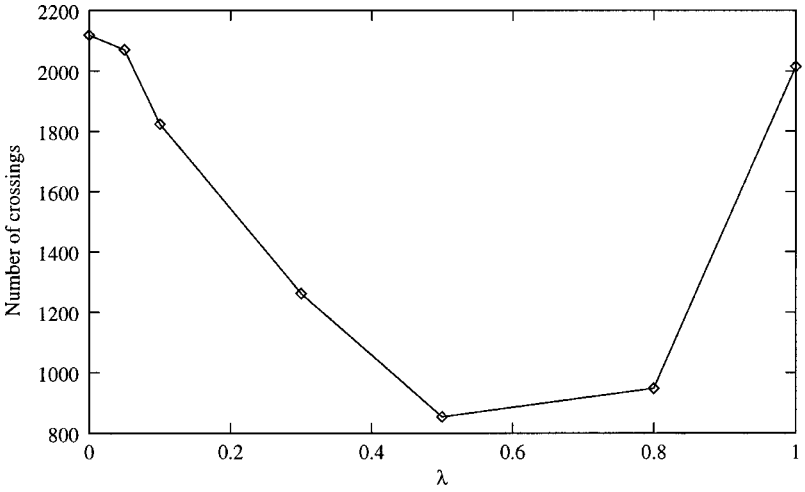

FIG. 4. Number of barrier crossing events as a function of λ from Brownian dynamics simulations of a test-particle in a one-dimensional double-well potential.

$$T_c = \sum_i \delta(t - t_i), \tag{10}$$

where $t_i; i = 1,2,...$ are now the instants of time at which the particle crosses in either direction the unstable equilibrium point at $x_{N+1} = 0$. The average number of barrier crossings were calculated by running ten simulations which differed only in the seeds for generating the distribution of an initial velocity assignment.

RESULTS AND DISCUSSION

Some qualitative inferences about the effect of the biasing force on the dynamics can be arrived at immediately from the form of Eq. (6). The behavior of the system would depend on the instantaneous relationship between f_μ and g_μ and also on the magnitude of λ which determines the degree of contribution of the biasing force to the net force acting on the system. If f_μ and g_μ happen to be closely correlated and of the same order of magnitude, then there literally occurs an enhancement of the systematic component of the force. But this can also be formally interpreted as an effective reduction of the temperature of the system, which consequently would make the system less able to cross barriers. On the other hand, if the two forces happen to be anticorrelated, the opposite will be expected to happen. This can be easily visualized as once a system gets into a slope of a potential minimum, its dynamics will rapidly drive it to the bottom, and hinder its escape by enhancing the downward force.

These general expectations were largely confirmed by quantitative calculations. The number of barrier crossings in a fixed interval of time as a function of λ is plotted in Fig. 4 for Brownian dynamics in one dimension. The plot shows

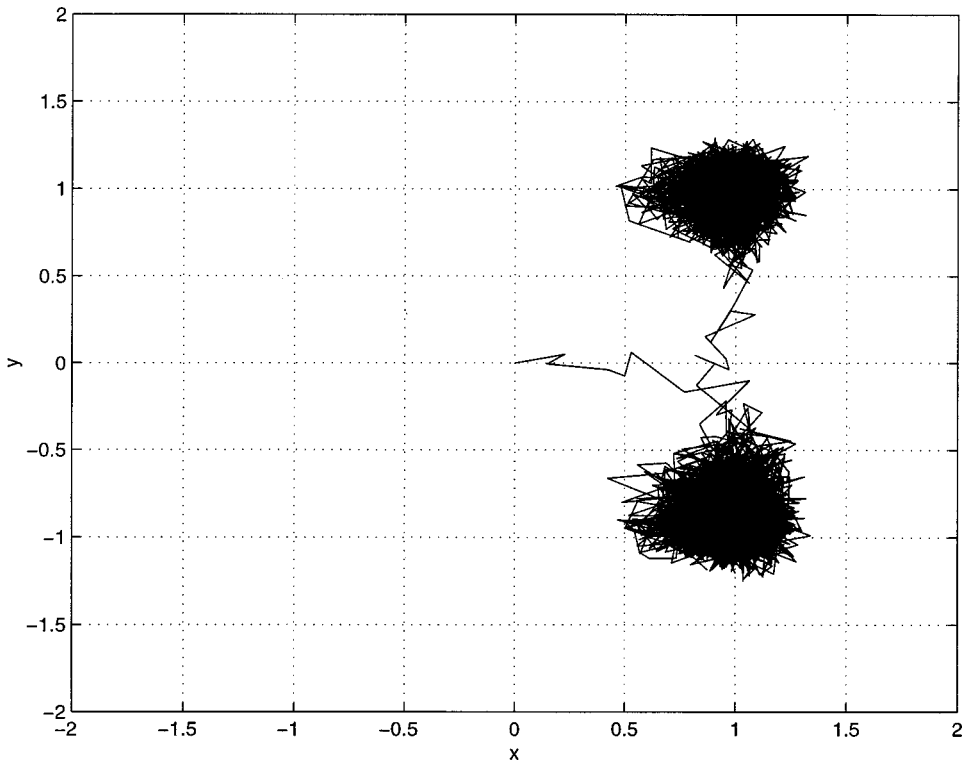

FIG. 5. Phase portrait from a Brownian dynamics simulation at $T = 0.1$.

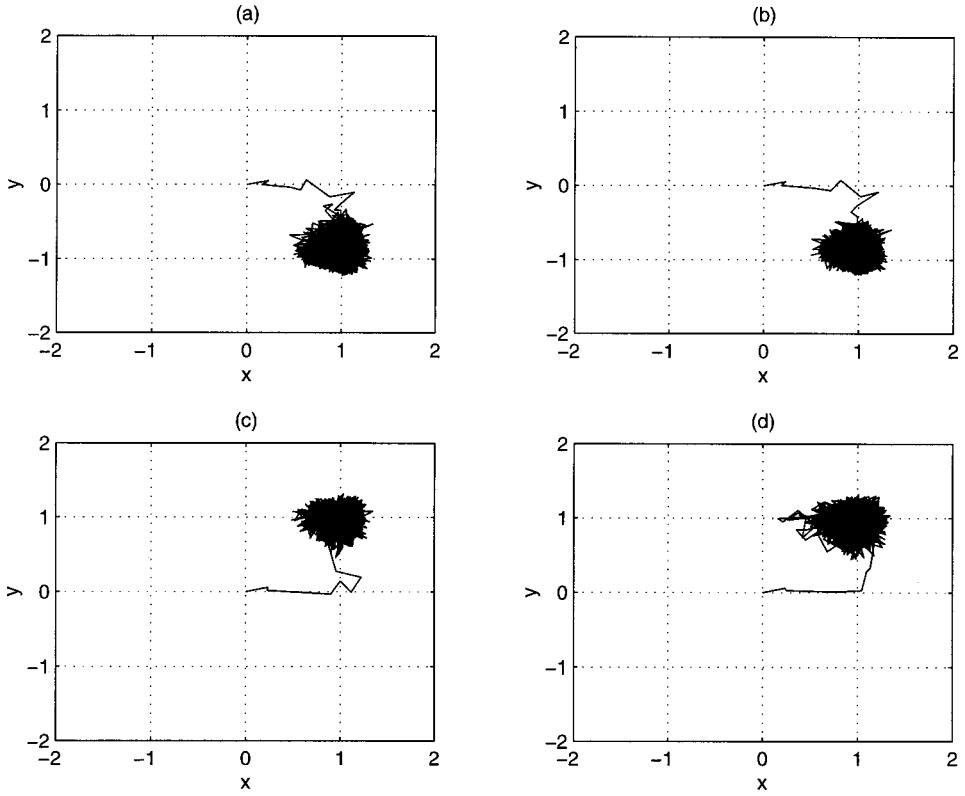

FIG. 6. Self-guided Brownian dynamics at $T=0.1$ with λ (a) 0.2, (b) 0.5, (c) 0.8, and (d) 1.0.

very clearly that the number of barrier crossing at first falls off with increasing λ. However, at large values of λ it starts to increase again.

Increasing the number of dimensions yields similar results. By suitably choosing the temperature and the self-diffusion coefficient we can make the system stay at a particular minimum in a two-dimensional energy landscape for a considerable period of time. Brownian dynamics simulation at one such temperature ($T=0.1$), leads to a trapping of the system in two of the four minima as shown in Fig. 5. Interestingly however, addition of the self-guiding term (with the averaging time $t_l=0.1$) in the Brownian dynamics at the same simulation condition did not introduce any enhanced sampling over the phase space at small values of λ. On the contrary, as shown in Fig. 6, it resulted in a longer trapping in a local minimum than in the conventional case. On further increasing λ, it was observed that the sampled space actually decreased to a certain point with an increase in λ after which it started to increase again. At a large value (e.g., $\lambda=2$) the configurational space is almost uniformly

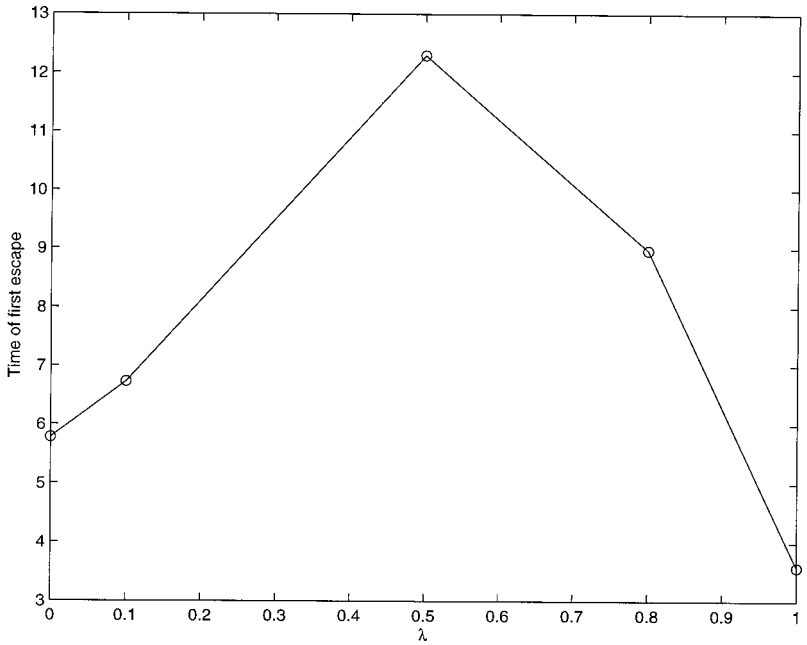

FIG. 7. Mean time of the first escape plotted against λ from Brownian dynamics simulations in the two-dimensional potential surface.

TABLE I. Correlation between f_x and g_x for different values of λ.

λ	Correlation coefficient
0.0	0.74
0.2	0.66
0.5	0.49
0.8	0.22
1.0	0.00

TABLE II. Correlation between f_x and g_x for different values of λ and t_l.

λ	$t_l=0.002$	$t_l=0.01$	$t_l=0.1$
0.00	1.00	1.00	0.97
0.02	1.00	1.00	0.96
0.05	1.00	1.00	0.94
0.08	1.00	1.00	0.93
0.10	1.00	1.00	0.93

sampled (not shown). This observation is supported quantitatively by the estimation of ''mean first escape time'' from a basin. In Fig. 7 we have plotted the mean first escape time of the system from the basin $(1, -1)$ at various values of λ. 1000 trajectories were sampled to calculate the mean for each λ. From the figure one can clearly see that with increasing λ, the mean time for making a jump over the barrier separating the starting basin from the rest increases at first, reaches a maximum, and then decreases.

To understand why larger values of λ lead to a ''better'' sampling, we looked at the correlation of the self-guiding force with the systematic component (Table I). As we can see, at small values of λ, the self-guiding force is much more correlated with the systematic force than at larger λs. Again at larger values of λ, the contribution of the biasing force to the dynamics is in itself considerable. As a result, one may think of the effect of self-guiding at larger λ as an effective increase in the inertia of motion.

Since the foregoing results clearly run contrary to that obtained by the original authors employing molecular dynamics simulations, it was necessary to examine the question in more detail to find out the origin of this difference. For that purpose we adopted a fully Hamiltonian model of a particle moving in a double-well potential and coupled to a chain of one-dimensional oscillators as was proposed very recently.[11] This model was designed to analyze the distribution of escape times of a bistable system embedded in a purely deterministic environment for comparing the behavior with its stochastic counterpart and it suits per-eminently our present purpose.

In Fig. 8 we have plotted the mean number of barrier crossings as a function of the parameter λ and the averaging time t_l for ten molecular dynamics simulations with $N+1$ oscillators where $N=100$. We find that for $t_l=0.1$ there occurs a monotonic increase in the barrier crossing rate with increasing λ as observed by the original authors. Surprisingly, however, for very small averaging time $t_l=0.002$ we observe a decrease in the average number of barrier crossings with λ as has been observed in the case of Brownian dynamics. At an intermediate value of $t_l=0.01$ there is a slight increase in the number of barrier crossings with λ. If we calculate the correlation between the systematic part of the force acting on the test-particle and the self-guiding force, we observe (Table II) that for small values of t_l these two forces are almost completely correlated while the self-guided term is moderately but significantly less correlated to the systematic force when $t_l=0.1$.

The above results for our deterministic model where the dynamics of the test-particle is subjected to a perturbation from its coupling to other oscillators made us interested about the behavior of the test-particle where no such perturbation was present. In the absence of the biasing term, the motion of the test-particle in the one-dimensional double-well potential is purely oscillatory. As we can see from Fig. 9, introduction of the self-guided term decreases the time period of this oscillation (or increases the frequency of barrier crossing) for all combinations of λ and t_l we investigated. However, this result was obtained without applying the velocity scaling procedure.

A rough analytical argument may be presented to understand the previous result. If we consider the dynamics of a particle in a simple harmonic potential, the equation of motion with the self-guided term can be written as

$$\frac{\partial^2 x(t)}{\partial t^2} = -x(t) - \frac{\lambda}{t_l}\int_{t-t_l}^{t} [x(\tau) - \lambda g(\tau)]\, d\tau. \tag{11}$$

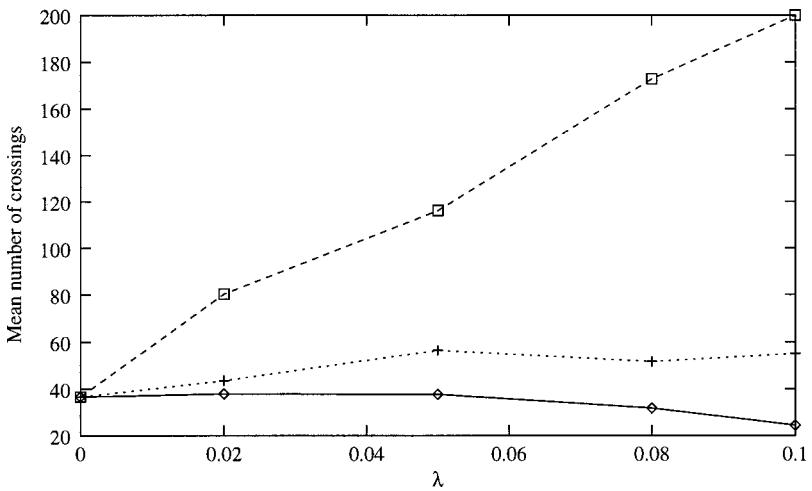

FIG. 8. Mean number of barrier crossing events plotted against λ from molecular dynamics simulations with $t_l=0.002$ (solid line), $t_l=0.01$ (dotted line), and $t_l=0.1$ (dashed line).

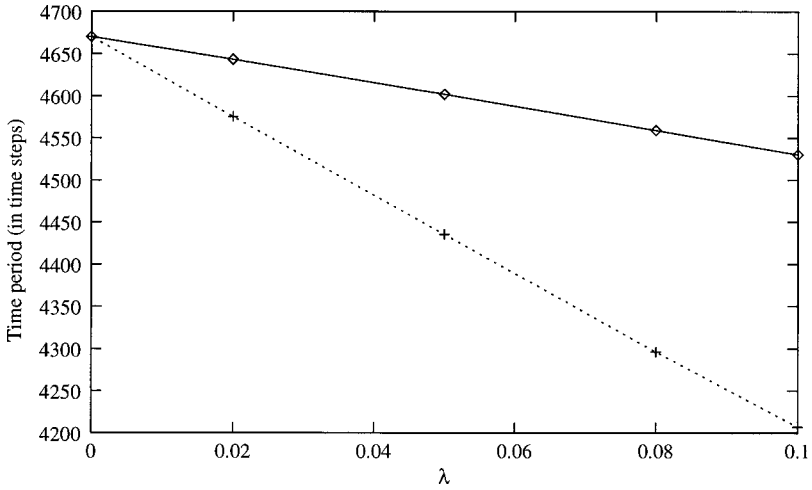

FIG. 9. The time period for a complete oscillation in the quartic potential as a function of λ from a self-guided molecular dynamics without velocity scaling. The solid line corresponds to $t_l = 0.002$ and the dotted line to $t_l = 0.1$.

Assuming λ to be so small that terms of second order can be neglected and further assuming t_l to be infinitesimally small, we can approximate the previous expression as

$$\frac{\partial^2 x}{\partial t^2} = -(1+\lambda)x, \tag{12}$$

which gives us an oscillator with a slightly increased frequency of oscillation for positive λ.

We propose to rationalize the above observations by suggesting that the difference in behavior between Brownian dynamics and molecular dynamics stems from the fact that in the diffusive regime all information about the velocity in the previous state is lost, i.e., the system does not possess an ''inertial memory.'' For such a situation, the introduction of a biasing force following the idea of self-guiding will not lead to any enhancement of sampling unless the bias is made exceedingly large. In that case, the biasing force becomes large and uncorrelated to the actual force, so that it alone can drive the system from basin to basin. However, in the case of molecular dynamics in the presence of coupling from other particles, the influence of the environment can be looked upon as a perturbation to the inertia of systematic motion. In that case, a very large degree of correlation between the systematic force and the biasing force produced a decrease in sampling with increasing λ as observed in the case of Brownian motion and even a moderate loss of correlation was sufficient to get into the regime where we get a monotonic increase in barrier crossing rate with λ. For the dynamics of the test-particle without any perturbation, the crossing rate increased even for complete correlation.

CONCLUSION

In the limit of no perturbation, the biasing always led to an enhanced rate of barrier crossing. However, in the other extreme, where the motion is such that all memory of the velocity is lost from the previous step, barrier crossing is enhanced only at a very high value of biasing. In the intermediate range of random perturbations, barrier crossing is decreased only for those functions which are too much correlated with the actual force. This gives us insight about the suitability of the self-guiding method and parameter selection for different dynamical simulation protocols.

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