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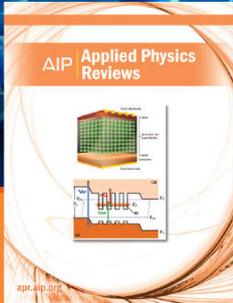
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# Kramers turnover: From energy diffusion to spatial diffusion using metadynamics

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We consider the rate of transition for a particle between two metastable states coupled to a thermal environment for various magnitudes of the coupling strength using the recently proposed infrequent metadynamics approach [P. Tiwary and M. Parrinello, *Phys. Rev. Lett.* **111**, 230602 (2013)]. We are interested in understanding how this approach for obtaining rate constants performs as the dynamics regime changes from energy diffusion to spatial diffusion. Reassuringly, we find that the approach works remarkably well for various coupling strengths in the strong coupling regime, and to some extent even in the weak coupling regime. © 2016 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4944577>]

## I. INTRODUCTION

It is well known that the dynamics of activated barrier crossing shows strong sensitivity to the strength of coupling to the environment.<sup>1</sup> Specifically, for a prototypical setup with two stable states separated by a barrier, the rate constant  $k$  for barrier crossing first increases, and then decreases, as the coupling to the environment increases. This non-monotonic behavior of the rate constant, known as Kramers' turnover, is of fundamental interest in chemical dynamics and manifests itself in a range of practical scenarios, including but not limited to isomerization reactions, protein folding and even excitation energy transfer in light-harvesting systems.<sup>2-4</sup> It has been thoroughly investigated through numerical, analytical, and experimental studies over the past few decades.<sup>1,5-8</sup> It is well accepted that in the low coupling regime the rate constant is small due to poor exchange of energy with the environment. Either the system rarely gains enough energy to cross the barrier or when it does so, it is unable to dissipate this energy and settle in the product state. On the other end, in the high coupling regime, spatial diffusion across the barrier top becomes the rate limiting factor, and increasing the environmental coupling leads to decrease in the rate constant.

In principle one can use molecular dynamics (MD) simulations to directly measure the rate constants for activated barrier crossing without making any assumptions on the nature of the dynamics regime. Here this coupling is generally implemented through a friction coefficient that quantifies the rate of collisions between the system of interest and a thermal bath. This however becomes a challenging task when the barrier height is much larger than the thermal energy  $k_B T$ , and it becomes difficult to observe sufficiently many or any barrier crossing events in MD given computer time limitations. To deal with this debilitating problem, over the years several enhanced sampling schemes have been proposed that accelerate barrier crossing events in a controllable manner. While many of these enhanced sampling methods concern

recovering the underlying free energy landscape, some are designed to calculate the actual rate of barrier crossing.<sup>9-14</sup>

In this short communication, we consider one such recently proposed method, the so-called "infrequent metadynamics" approach,<sup>14,15</sup> which has recently been applied successfully to obtain rate constants in a variety of complex molecular systems,<sup>16,17</sup> and is briefly summarized in Sec. II. Given the potential benefit of this approach and its increasing popularity, in this work we explore its robustness in obtaining rate constants for a model 2-state system<sup>18</sup> with respect to varying coupling strength to a thermal bath implemented via Langevin dynamics.<sup>19</sup> Through a large number of independent simulations, we identify the environmental coupling regime in which the dynamics from infrequent metadynamics is correct, by comparing against much longer unbiased MD runs. We find that infrequent metadynamics gives correct rates across several orders of magnitude variation in the environmental coupling, as long as one stays in the high coupling regime. It also reproduces the pronounced change in rate associated with Kramers' turnover. It tends to become less reliable as the coupling constant is made very low and the system enters the deeply underdamped regime. Thankfully, most biomolecular systems, which are the target systems for the method,<sup>16,17</sup> involve large numbers of solvent atoms executing rapid thermal motions where one expects the moderate to high friction regime to be applicable. As we find in this work, the infrequent metadynamics approach is indeed reliable in this regime.

## II. DYNAMICS FROM INFREQUENT METADYNAMICS

Metadynamics is an enhanced sampling approach that begins by identifying a small number of slowly changing order parameters, called collective variables (CVs).<sup>20,21</sup> By periodically adding repulsive bias in the regions of CV space as they are visited, the system is encouraged to escape stable free energy minima where it would normally be trapped. The traditional objective of a metadynamics run is to recover the underlying true free energy surface as a function

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of the deposited bias.<sup>20</sup> Recently, Tiwary and co-workers extended the scope of metadynamics by showing how to extract unbiased rates from biased ones with minimal extra computational burden,<sup>14,15</sup> inspired by works such as Refs. 10 and 11. The central idea was to deposit bias infrequently enough compared to the time spent in the transition state regions. Through this “infrequent metadynamics” approach one increases the likelihood of not corrupting the transition states through the course of metadynamics, thus preserving the sequence of transitions between stable states. One can then access the acceleration of transition rates achieved through biasing by appealing to generalized transition state theory<sup>1</sup> and calculating the following simple running average:<sup>14</sup>

$$\alpha = \langle e^{\beta V(s,t)} \rangle_t, \quad (1)$$

where  $s$  is the collective variable being biased,  $\beta = \frac{1}{k_B T}$  is the inverse temperature,  $V(s,t)$  is the bias experienced at time  $t$ , and the subscript  $t$  indicates averaging under the time-dependent potential.

This approach assumes that one has the correct slow order parameters or CVs that can demarcate all relevant stable states of interest. Whether this is the case or not can be verified *a posteriori* by checking if the transition time statistics conforms to a Poisson distribution.<sup>15</sup> The current work assumes one has the right order parameters or collective variables for the problem at hand. For the model potential considered in this work (Sec. III), this is not a problem. For more complicated systems one can identify such CVs in principle through a recently proposed method.<sup>22</sup>

### III. SIMULATION DETAILS

We consider a model 2-state potential (Fig. 1(a)) introduced by De Leon and Berne,<sup>18</sup> which has been the subject of numerous similar studies<sup>1,23</sup> in the past. It is given by

$$V(x, y) = 4y^2(y^2 - 1)e^{-4.485x} + 10(1 - e^{-1.95x})^2 + 1. \quad (2)$$

All units of energy and mass were defined in terms of Eq. (2). Let  $q = (x, y)$  denote the configurational coordinates of the system, and  $m$  be the mass. All our simulations are performed with  $m = 8$  u and temperature  $k_B T = 0.1$  u, with Newton’s laws of motion integrated per Langevin dynamics with a time step 0.05 u

$$m\ddot{q} + \frac{dV(q)}{dq} + m\gamma\dot{q} = F(t), \quad (3)$$

where  $\gamma$  is the friction coefficient,  $F(t)$  is a Gaussian random noise with mean zero and correlation function  $\langle F(t)F(t') \rangle = \frac{2m\gamma}{\beta} \delta(t - t')$ . There are many available schemes for implementing Langevin dynamics—we use the one from Ref. 19. For unbiased MD as well as metadynamics, the simulations were performed separately for 11 different values of the friction coefficient  $\gamma$  between  $10^{-4}$  and 10. The bias was constructed as a function of the spatial coordinate  $y$ . The well-tempered flavor of metadynamics<sup>21</sup> was used, with the so-called biasing factor that controls the gradual decay of Gaussian amplitude set to 6. An initial Gaussian height of  $0.1 k_B T$  and width of 0.1 u were used. Two different biasing

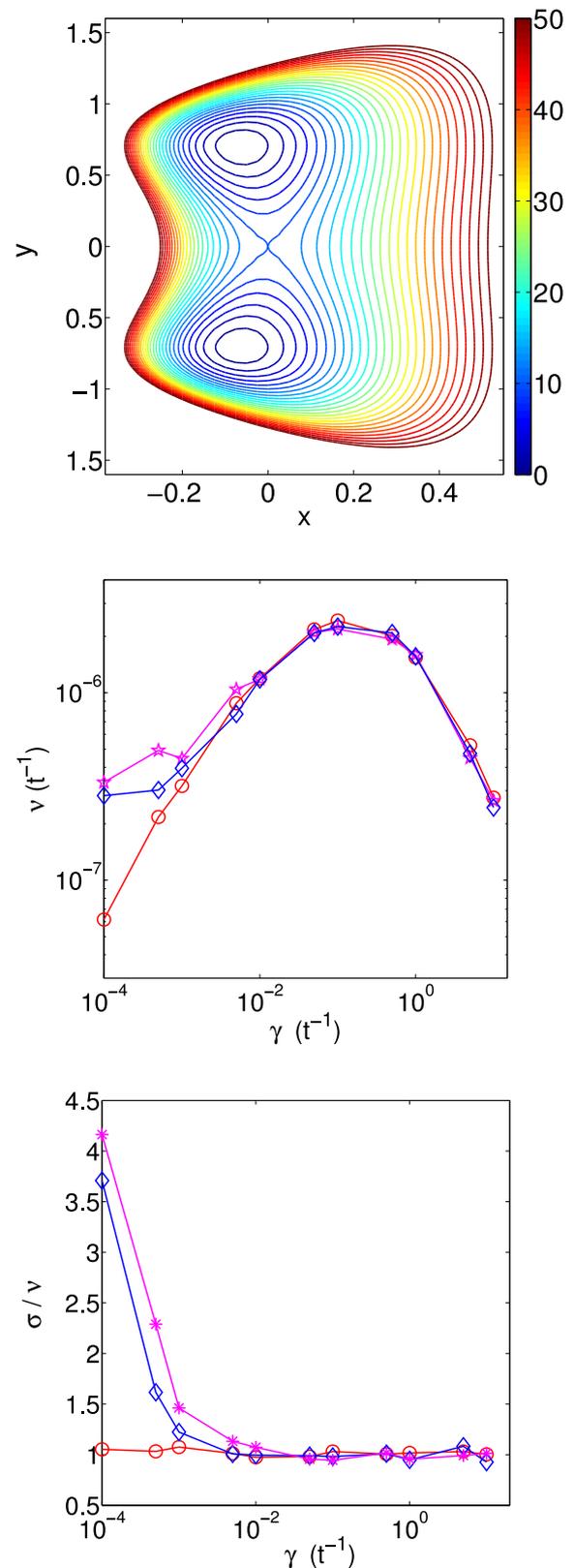


FIG. 1. (a) The 2-state model potential considered in this work, as described in Sec. III and in Ref. 18. All energies are in  $k_B T$  units, with contours spaced every  $2 k_B T$ . The barrier here is approximately  $10 k_B T$ . (b) The rate  $\nu$  of transitions between the two stable states in (a), as a function of the friction coefficient  $\gamma$  in Eq. (3). (c) Standard error in rate ( $\sigma$ ) divided by the average rate ( $\nu$ ) for each of the data points in (b). In (b) and (c), the red circles correspond to unbiased MD estimates. The blue diamonds and magenta stars are for the slow deposition and fast deposition schemes, respectively. All units are in accordance with Eq. (2).

frequencies were used to ascertain sensitivity to the biasing stride—once every 20 000 integration steps and once every 100 000 steps. These will be denoted as the fast and slow deposition schemes, respectively.

#### IV. RESULTS AND DISCUSSION

In Fig. 1(b), we provide the transition rate  $\nu$  as a function of the friction coefficient  $\gamma$  in Eq. (3), which is kept same for both  $x$  and  $y$  coordinates. Fig. 1(c) gives the corresponding errors in rates. The rate was calculated as  $\nu = 1/\langle t \rangle$  where  $\langle t \rangle$  is the average residence time in either of the basins. To filter out spurious recrossing events, we used a minimum residence time criterion of  $10^4$  time units, or  $2 \times 10^5$  integration steps, to count a transition event as successful. This criterion, which is similar to checking for a plateau region in the reactive flux formalism,<sup>9</sup> was enforced uniformly across unbiased MD and both the metadynamics schemes. While the absolute magnitude of the rate constant itself shows some sensitivity to the employed minimum residence time cut-off, the conclusions of this work as described below were found to be very robust to this choice. The metadynamics runs with the slow and fast deposition schemes corresponded to acceleration as per Eq. (1) relative to unbiased MD, of approximately 35 and 45, respectively. Naturally, the simulation lengths for the unbiased MD runs were thus correspondingly much longer. The following salient features can be seen from Fig. 1:

1. Both the deposition schemes for metadynamics agree with unbiased MD in the magnitude of the friction  $\gamma$  at which turnover in rate occurs, and the dynamics switches from energy diffusion to spatial diffusion.
2. All three schemes, viz., unbiased MD, metadynamics with slow bias deposition and with fast bias deposition agree very well across the spatial diffusion regime, which is not entirely surprising given that the bias was constructed explicitly as a function of the spatial coordinate  $y$ .
3. What is more surprising is that MD and metadynamics continue to agree to some extent even in the energy diffusion regime (i.e., low friction  $\gamma$ ). As the friction  $\gamma$  is continued to reduce, at some point the rate curves from both the fast and slow deposition schemes cleave off the curve from unbiased MD. The cleavage occurs earlier (that is at higher friction) for the fast deposition scheme than for the slow deposition scheme. This brings out one of the key requirements for infrequent metadynamics to work: the biasing time interval should be larger than the relaxation time due to the solvent, or the relaxation time associated to any intramolecular vibrational relaxation (IVR). Also, the slow deposition scheme is less likely to corrupt dynamical trajectories that take a long time to commit to either of the two stable states even when they have crossed the barrier.
4. Fig. 1(c) shows the standard error in the rates scaled by corresponding mean rates for various simulation protocols. This ratio should be one for a Poisson distribution.<sup>15</sup> For unbiased MD, this stays the case across the friction range. For metadynamics, one can see corruption of the rates as this ratio becomes larger than one. Here as well larger errors can be seen at higher friction for the fast deposition case.

Thus, to summarize, in this short communication we demonstrate through a numerical example that infrequent metadynamics performs remarkably well in obtaining the rate constant for various environmental coupling strengths, especially in the moderate to high friction regime, which is the regime of interest for most solvated biomolecular systems. At very low frictions, the method fails because the biasing time interval is comparable to the time scale for IVR or solvent relaxation. Obviously by making the biasing time sufficiently long we could capture both the low friction and long IVR time more accurately but then we would lose the speedup due to metadynamics. In the limit of very low biasing times we would recover the results of pure MD. Alternatively, this might be circumvented if the biasing potential was to include a reaction coordinate that quantifies energy transfer between various internal and/or solvent degrees of freedom.

Finally, we would like to suggest that such a test that ascertains the accuracy of rates across dynamics regime change be performed on any method before it is judged to be trustworthy as a tool for enhancing molecular dynamics and obtaining rate constants. We would like to point out that Ref. 23 provides a rich collection of landscapes and dynamical conditions under which the infrequent metadynamics approach, or any other enhanced sampling approach for rates could be further tested for regimes of applicability.

#### ACKNOWLEDGMENTS

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