

# Metadynamics with Adaptive Gaussians

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## S Supporting Information

**ABSTRACT:** Metadynamics is an established sampling method aimed at reconstructing the free-energy surface relative to a set of appropriately chosen collective variables. In standard metadynamics, the free-energy surface is filled by the addition of Gaussian potentials of preassigned and typically diagonal covariance. Asymptotically the free-energy surface is proportional to the bias deposited. Here, we consider the possibility of using Gaussians whose variance is adjusted on the fly to the local properties of the free-energy surface. We suggest two different prescriptions: one is based on the local diffusivity and the other on the local geometrical properties. We further examine the problem of extracting the free-energy surface when using adaptive Gaussians. We show that the standard relation between the bias and the free energy does not hold. In the limit of narrow Gaussians an explicit correction can be evaluated. In the general case, we propose to use instead a relation between bias and free energy borrowed from umbrella sampling. This relation holds for all kinds of incrementally deposited bias. We illustrate on the case of alanine dipeptide the advantage of using adaptive Gaussians in conjunction with the new free-energy estimator both in terms of accuracy and speed of convergence.

## 1. INTRODUCTION

The problem of sampling complex energy surfaces, characterized by metastable states separated by large energy barriers, has recently received considerable attention. A list that is by no means exhaustive of the possible remedies suggested includes transition path sampling,<sup>1</sup> umbrella sampling,<sup>2,3</sup> local elevation,<sup>4</sup> Wang–Landau,<sup>5</sup> adaptive biasing force,<sup>6</sup> metadynamics,<sup>7–10</sup> and self-healing umbrella sampling.<sup>11</sup>

We focus here on metadynamics (MetaD).<sup>7,8</sup> In this approach, one starts by identifying a set of appropriately chosen collective variables  $s$  which are a function of the microscopic variables  $q$ . In order to accelerate sampling, a bias potential is dynamically added during the simulation. The bias has the effect of helping the system to overcome large free-energy barriers so as to accelerate sampling. Asymptotically, the negative of the bias provides an estimate of the free energy  $F(s)$  associated with the collective variable  $s$ . The estimate has been demonstrated to be free of systematic errors, if the CVs are properly chosen.<sup>9</sup>

Metadynamics has been successfully used in several different contexts; for a recent review, see for instance ref 10. In most cases, the bias is constructed by periodically adding a repulsive Gaussian potential<sup>4</sup> which is a function of the  $s$ . This implies defining the height and width of the Gaussians. The first is related to the energy deposition rate, while the latter is taken small enough to resolve the free-energy surface features. Prescriptions on how to choose these parameters have been given, and the dependence of the statistical error on their choice has been discussed.<sup>8</sup> Still, one is not guaranteed *a priori* of making the best choice.

More recently, a new flavor of metadynamics has been introduced which goes under the name of well-tempered metadynamics (WTMetaD).<sup>12</sup> In WTMetaD, the speed at which the bias is added decreases during the simulation. WTMetaD maintains the property that the asymptotic bias is related to  $F(s)$  by a simple relation, but, at variance with standard metadynamics, the final free-energy estimate converges to a definite limit.

A useful property of WTMetaD is that the dependence of the final result on the speed with which the bias grows is smaller than in standard metadynamics,<sup>12</sup> reducing the impact of an improper choice of this parameter. Here, we want to move further toward making the method even more efficient and robust with respect to parameters choice. A natural step in this direction is to add the possibility of adapting the Gaussian width to the local free energy so as to speed up sampling. For instance, a free-energy surface may present minima with rather different curvature, and a Gaussian width optimal for one might be not appropriate for another (see the Supporting Information). This problem is amplified in the case of CVs that are highly nonlinear functions of the atomic coordinates.

In the past, this need was recognized. Therefore, *ad hoc* solutions for speeding up free-energy surface exploration were developed,<sup>13</sup> and some form of metadynamics that uses adaptive Gaussians was implemented in publicly available codes.<sup>14</sup> Very recently, Tribello et al.<sup>15</sup> also used adaptive Gaussians in a related but distinct context. However, the effect

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of these choices on the free-energy reconstruction has never been systematically investigated.

Another common assumption in multidimensional MetaD simulations is to adopt Gaussian functions whose axes are aligned to the chosen CVs, i.e., with a diagonal covariance matrix. This is clearly a simplification which reduces the number of input parameters, but an optimal choice might require Gaussian axes which are not aligned to the CVs. This was pointed out in ref 13 and successively has been used for crystal-structure prediction.<sup>16,17</sup>

In this paper, we discuss the possibility of performing metadynamics simulations using multivariate Gaussian potentials with a full covariance matrix computed on the fly. We first introduce two possible different schemes for choosing the shape and width of the Gaussian potentials. One is dynamical and based on the mean square displacement of the CVs in a predetermined time interval. The other is geometrical and based on the local mean square displacement of the CVs due to a hypothetical change in the microscopic coordinates. Subsequently, we observed that the adoption of either of these two position-dependent covariances requires modifying the free-energy estimator in order to reconstruct accurately the free-energy landscape. Furthermore, we show that this new scheme applies also when the added Gaussian potentials or some other chosen form of potentials are coarser than the underlying free energy. The algorithms and their efficiency are numerically tested in the standard case of alanine dipeptide in a vacuum. Details of the simulations and error calculations are discussed in the Appendix.

## 2. METHODS

**2.1. Metadynamics.** In MetaD, a time-dependent bias potential  $V(s,t)$  is used to discourage the system from visiting already explored regions in the CVs space.<sup>7,12</sup> At the beginning of the simulation, the bias is everywhere equal to zero. Subsequently, it is evolved according to the following expression:

$$\dot{V}(s, t) = \omega e^{-V(s(t),t)/\Delta T} g(s, s(t)) \quad (1)$$

where  $g(s,s(t))$  is a short-ranged kernel function.

Here,  $\Delta T$  is an energy which can be used to tune the region of free energy explored, and  $\omega$  is the initial filling rate. It has been shown in ref 12 that for large times the bias is related to the free energy by

$$F(s) = -\lim_{t \rightarrow \infty} \frac{\Delta T + T}{\Delta T} [V(s, t) - C(t)] \quad (2)$$

where  $C(t)$  does not depend on  $s$ . We notice here that even if  $C(t)$  eventually diverges, its impact on the result is completely irrelevant as it disappears in any free-energy difference calculation. The limiting behavior of  $C(t)$  is discussed in Appendix A.

These two expressions cover both the case of WMetaD<sup>12</sup> (where  $\Delta T$  is finite and is an additional tuning parameter) and non-WMetaD,<sup>7</sup> which is simply recovered in the limit  $\Delta T \rightarrow \infty$  and corresponds to the case where the filling rate is kept constant during the simulation. The properties of eq 1 were extensively discussed in ref 12. Equation 2 is of practical use since it offers an estimate of the free energy up to an arbitrary constant if one assumes its validity also at finite time:

$$\tilde{F}(s, t) = -\frac{\Delta T + T}{\Delta T} [V(s, t) - C(t)] \quad (3)$$

In most practical applications, the kernel  $g(s,s(t))$  of eq 1 has been replaced by a smooth function of the CVs, typically a product of one-dimensional Gaussians. We choose here a generic multivariate Gaussian function:

$$\begin{aligned} \dot{V}(s, t) = & \omega e^{-V(s(t),t)/\Delta T} \\ & \times \exp \left( -\frac{1}{2} \sum_{ij} [s_i - s_i(t)] \sigma_{ij}^{-2} [s_j - s_j(t)] \right) \end{aligned} \quad (4)$$

Here,  $\sigma_{ij}$  determines the shape of the Gaussian potential. In conventional MetaD simulations,  $\sigma_{ij}$  have almost always been assumed diagonal, with only a few exceptions.<sup>13,15–17</sup> We stress once again that in all of these cases MetaD was not employed to estimate the underlying free energy but only to speed up the exploration of configuration space, and no attention has been paid to the effect of these protocols on the free-energy reconstruction.

Passing from a diagonal  $\sigma_{ij}$  to a nondiagonal one increases the number of parameters that have to be chosen when setting up the simulation, so that it would be convenient to give a prescription that simplifies this choice. In standard MetaD, the diagonal elements of  $\sigma_{ij}$  are obtained by computing the CV standard deviation during a short preliminary simulation. A simple extension is to consider also the correlation between different variables

$$\sigma_{ij}^2 \propto \langle \Delta s_i \Delta s_j \rangle \quad (5)$$

This choice is completely invariant with respect to an arbitrary linear transformation in the CV space and reduces to a diagonal  $\sigma_{ij}$  by a suitable transformation.<sup>16</sup> In addition, it allows easy mixing of CVs of different units and natures. However, an optimal  $\sigma_{ij}$  over the entire CVs domain requires that is made position dependent. Thus, we shall still use eq 5 to estimate the Gaussian covariance, but in the same spirit of ref 13, we shall give a time dependent estimation of  $\langle \Delta s_i \Delta s_j \rangle$  so as to reflect the local properties of the free energy. We finally note that the use of eq 5 still preserves the property of invariance relative to linear combination of the  $s$  variables. However, the covariance matrix cannot be reduced to a diagonal form everywhere by means of a single linear transformation of the CVs since the matrices  $\sigma_{ij}$  at different times or positions cannot be expected in general to commute.

**2.2. Dynamically-Adapted Gaussians.** To define a time-dependent adaptive covariance at time  $t$ , we compute the average value of the CVs and all of the elements of the covariance matrix from the last part of the trajectory. The center of the Gaussian is placed at the computed average value. To select the segment of trajectory over which we perform the average, we found it convenient to introduce an exponential weighting function with characteristic decay time  $\tau_D$ , such that the Gaussians' centers  $\bar{s}_i(t)$  and their covariances at time  $t$  are given by

$$\bar{s}_i(t) = \frac{1}{\tau_D} \int_0^t dt' s_i(t') e^{-(t-t')/\tau_D} \quad (6)$$

and

$$\begin{aligned} \sigma_{ij}^2(t) = & \frac{1}{\tau_D} \int_0^t dt' [s_i(t') - \bar{s}_i(t')][s_j(t') - \bar{s}_j(t')] \\ & \times e^{-(t-t')/\tau_D} \end{aligned} \quad (7)$$

With this choice, the Gaussian location and covariance change smoothly and can be very easily evaluated. To this effect, we take the time derivative of eqs 6 and 7

$$\dot{\bar{s}}_i(t) = \frac{s_i(t) - \bar{s}_i(t)}{\tau_D} \quad (8)$$

$$\dot{\sigma}_{ij}^2(t) = \frac{[s_i(t) - \bar{s}_i(t)][s_j(t) - \bar{s}_j(t)] - \sigma_{ij}^2(t)}{\tau_D} \quad (9)$$

and then consider  $\bar{s}_i(t)$  and  $\sigma_{ij}^2(t)$  as additional variables to be evolved together with the system dynamics. Integrating eqs 8 and 9 with the initial conditions  $\bar{s}_i(0) = s_i(0)$  and  $\sigma_{ij}^2(0) = 0$ , the values of  $\bar{s}_i(t)$  and  $\sigma_{ij}^2(t)$  as defined by eqs 6 and 7 are recovered. We name this scheme *dynamically adapted* (DA). Using partial time averages to determine  $\sigma^2(t)$  is somewhat natural, and it has the practical benefit that only one parameter  $\tau_D$  determines the whole covariance matrix.

Within this scheme,  $\tau_D$  determines the time window which is used to estimate the CV fluctuations and thus to choose the Gaussian width. It is instructive to see how the latter depends on the dynamical properties of the system at least in the simplified case of Langevin dynamics (see the example in the Supporting Information). In this case, two regimes can be identified, for short and long values of the simulation time. At the beginning of the simulation, the dynamics is still stuck in the metastable minima. If  $\tau_D$  is larger than the typical autocorrelation time of the CV, the Gaussian shape will be equal to the shape of the corresponding free-energy minimum, thus providing an optimal filling. At the end of the simulation, when the barriers have been smoothed out by the adaptive bias, the dynamics is close to a free diffusion, with a diffusion coefficient which is possibly position dependent. Simple dimensional considerations can be used to show that the computed  $\sigma_{ij}^2$  matrix becomes proportional to the position-dependent diffusion tensor  $D_{ij}(s(t))$ , which has a relevant role in describing many important phenomena.<sup>18</sup>

**2.3. Geometry-Adapted Gaussians.** We shall now discuss an alternative protocol for choosing the  $\sigma$  matrices. Our starting point will be again eq 5. For small displacements of the microscopic variables  $q$ , the associated change in each CV can be linearly approximated as

$$\Delta s_i \approx \sum_{\alpha} \frac{\partial s_i}{\partial q_{\alpha}} \Delta q_{\alpha} \quad (10)$$

Then, in this approximation, it can be easily seen that the CV's covariance is linearly related to that of the atomic displacements  $\langle \Delta q_{\alpha} \Delta q_{\beta} \rangle$ . If we assume these to be Gaussian distributed with standard deviation  $\sigma_G$ , we have  $\langle \Delta q_{\alpha} \Delta q_{\beta} \rangle = \delta_{\alpha\beta} \sigma_G^2$  leading to

$$\langle \Delta s_i \Delta s_j \rangle \approx \sigma_G^2 \sum_{\alpha} \frac{\partial s_i}{\partial q_{\alpha}} \frac{\partial s_j}{\partial q_{\alpha}} \quad (11)$$

We use this expression to define the shape of the Gaussian covariance via the Gram matrix:

$$\sigma_{ij}^2(q) = \sigma_G^2 \sum_{\alpha} \frac{\partial s_i}{\partial q_{\alpha}} \frac{\partial s_j}{\partial q_{\alpha}} \quad (12)$$

With this choice,  $\sigma^2(q)$  depends explicitly on the microscopic variables  $q$ . We shall refer to this case as *geometry-adapted* (GA). As in the DA case, only one parameter suffices to determine the whole covariance matrix. We note that in MetaD the Gaussian

spread plays a role similar to that of the histogram bin size for other methods and determines which configurations are considered as equivalent. Thus, here we are assuming as equivalent all the microscopic configurations whose root square distance of the atoms involved in the CVs is within  $\sigma_G$ , making it possible for the choice of  $\sigma_G$  to be guided by physical considerations. For instance, if one were to choose a different set of CVs, still the choice of  $\sigma$  would be determined by the typical atomic displacements.

Similarly to the DA scheme, the GA one is invariant with respect to linear transformations of the CVs.

### 3. FREE-ENERGY ESTIMATION

One of the most interesting features of metadynamics is the link it establishes between the free-energy surface and the bias, in both its classical and well-tempered versions. Having changed the protocol of Gaussians deposition, it is crucial to establish such a link in the case of Gaussians of variable covariance.

**3.1. Small-Width Limit.** We consider first the case in which the Gaussians have a size smaller than the relevant features in the free-energy surface, as normally done in MetaD. This was the assumption of ref 12, where one went as far as to assimilate the Gaussians to  $\delta$  functions.

Within our schemes, this limit can be achieved by choosing  $\tau_D$  or  $\sigma_G$  small enough. In this regime, for the DA scheme, one can also neglect the difference between the actual position  $s$  and the center of the deposited Gaussian  $\bar{s}$ . Therefore the only adjustment necessary is to take into account the fact that the change in covariance induces a change in Gaussians' volume. Thus, in eq 1, we replace the kernel  $g(s, s(t))$  with a Dirac delta with the same normalization,  $((2\pi)^d)^{1/2} \det \sigma \delta(s - s(t))$ , where  $\sigma$  is a function either of the trajectory in CVs' space (DA scheme) or of the microscopic coordinates at a specific time (GA scheme) and  $d$  is the number of CVs:

$$\dot{V}(s, t) = \omega e^{-V(s(t), t)/\Delta T} \sqrt{(2\pi)^d \det \sigma} \delta(s - s(t)) \quad (13)$$

As in ref 12, we notice that for large times the probability distribution becomes  $P(s, t) \propto \exp(-(F(s) + V(s, t))/T)$  and one has

$$\begin{aligned} \dot{V}(s, t) &= \omega e^{-V(s, t)/\Delta T} \sqrt{(2\pi)^d} \langle \det \sigma \rangle_s P(s, t) \\ &\propto e^{-V(s, t)/\Delta T} \langle \det \sigma \rangle_s e^{-[F(s) + V(s, t)]/T} \end{aligned} \quad (14)$$

where the average  $\langle \det \sigma \rangle_s$  is taken in the canonical ensemble at a fixed value of the Gaussian center. Now, setting  $\dot{V} = C(t)$  in the last equation, where  $C(t)$  is constant with respect to the CVs, we find that the asymptotic solution for  $V(s, t)$  is

$$\lim_{t \rightarrow \infty} V(s, t) = -\frac{\Delta T}{\Delta T + T} [F(s) - T \ln \langle \det \sigma \rangle_s] + C(t) \quad (15)$$

This means that the bias is no longer proportional to  $F(s)$  as in eq 2 but rather to

$$G(s) = F(s) - T \ln \langle \det \sigma \rangle_s \quad (16)$$

In the case of the GA scheme of section 2.3,  $G(s)$  turns out to be the gauge invariant free-energy discussed in refs 19–21, which is not changed by an arbitrary nonlinear monotonic transformation of the CVs. Instead, in the DA case of section 2.2, when  $\tau_D$  is chosen so that  $\sigma$  is proportional to the diffusion matrix, our bias potential is closely connected with that used in

flux-tempered metadynamics,<sup>22</sup> which is also gauge invariant and has been designed to optimize the round trip time.

While gauge invariance is aesthetically pleasing, it does not bring particular advantages since for physical applications it is  $F(s)$  that is needed. This can be simply obtained by rewriting eq 15 as

$$F(s) = -\lim_{t \rightarrow \infty} \frac{\Delta T + T}{\Delta T} [V(s, t) - C(t)] + T \ln \langle \det \sigma \rangle_s \quad (17)$$

which is the appropriate generalization of eq 2 in the case of small adaptive Gaussians.

**3.2. Free Energies from Reweighting.** As discussed in the previous sections, for nonstandard biasing protocols, the relationship between the asymptotic bias and the underlying free-energy landscape is not known *a priori*. Only in the small width limit is it possible to estimate explicitly the correction of eq 17. However, it would be nice to have an estimator that is valid for large Gaussians. This is provided by the relation:

$$\begin{aligned} \tilde{F}_N(s, t) &= -T \ln N(s, t) - V(s, t) \\ &+ T \ln \int ds' N(s', t) \end{aligned} \quad (18)$$

where  $N(s, t)$  is the accumulated histogram of the variable  $s$  up to time  $t$ . If the bias is time-independent, this relation is strictly true and is normally used in umbrella sampling. In this present context it is valid only for large times when  $V(s, t)$  has converged. More precisely it is only necessary that the rate of bias deposition goes to zero sufficiently rapidly. Therefore, it will be valid whether the Gaussian width is small or large and whether the width is determined by dynamics or geometry.

This relation was also used in deriving a free-energy estimator for WTMetaD,<sup>12</sup> where this expression was manipulated in a manner similar to that in section 3.1, leading to the estimator in eq 3. However,  $\tilde{F}_N(s, t)$  is more generally valid and gives a correct estimate of free energy even when adaptive Gaussians are used. In the following, we will show how this new estimator can be of use in a practical case.

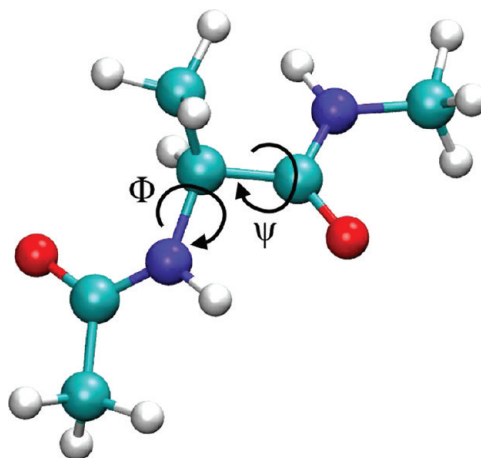
The case of non-WT metadynamics (i.e., for  $\Delta T \rightarrow \infty$ ) where the bias oscillates in the long time limit needs separate consideration and will be discussed elsewhere.

## 4. EXAMPLES

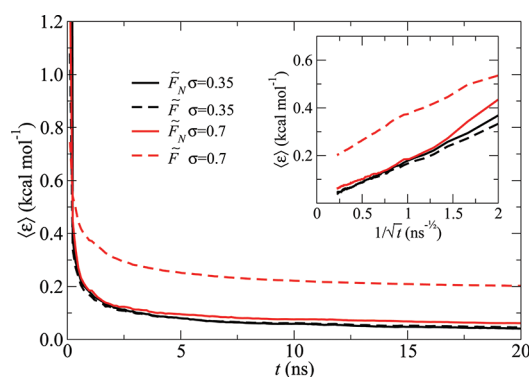
**4.1. Narrow and Wide Gaussians.** Before discussing the performance of the adaptive Gaussians, we shall first validate the estimator of eq 18 when using standard WTMetaD and compare two very different choices of Gaussian width. In this way, we show that it is advantageous to use eq 18 even when using Gaussians with fixed covariance.

To this effect, we performed a number of WTMetaD simulations of alanine dipeptide in a vacuum (see Figure 1) using as collective variables the two Ramachandran<sup>24</sup> dihedral angles  $\Phi$  and  $\Psi$ . The initial Gaussian height was chosen to be  $0.287 \text{ kcal mol}^{-1}$ , and Gaussian potentials were deposited every 120 fs, corresponding to an energy deposition rate of  $2.39 \times 10^{-3} \text{ kcal mol}^{-1} \text{ fs}^{-1}$ . The  $\Delta T$  parameter for WTMetaD was set to 1200 K. Other technical details can be found in Appendix B.

We first performed a long calculation to obtain a reference free-energy landscape. This was done in two steps: we performed a 5-ns-long WTMetaD run with a Gaussian width  $\sigma = 0.35 \text{ rad}$  for both  $\Phi$  and  $\Psi$ , and the bias thus accumulated was then kept constant in a long (1  $\mu\text{s}$ ) biased simulation.



**Figure 1.** Molecular sketch of alanine dipeptide with the Ramachandran dihedral angles  $\Phi$  and  $\Psi$ . This graphics was produced with VMD.<sup>23</sup>

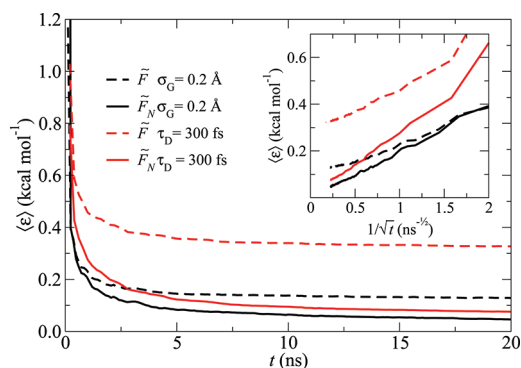


**Figure 2.** The estimate of the average error as a function of simulation time for alanine dipeptide in a vacuum. The average error was calculated through a set of 100 runs and averaged every 120 ps. The effect of adopting  $\tilde{F}_N$  of eq 18 for two different choices of  $\sigma$  is compared to the choice of  $\tilde{F}$  of eq 3. It is possible to appreciate that eq 18 always delivers results that are comparable to those of eq 3 or better, when large Gaussians are adopted. In the inset, the time dependence of the error that decreases linearly with  $1/\sqrt{t}$  is shown predicting an error that goes to zero for infinite time. On the contrary, for large Gaussians, the standard estimate is not able to resolve the features of the free energy, resulting in a significant residual error even for infinite time.

Then, by using eq 18, which is exact for a static bias, we obtained the reference free energy. The error of the reference landscape was estimated by comparing the free energy derived from the histogram from the first and the second half of the simulation and was obtained using the procedure reported in Appendix C. The error is approximately  $0.01 \text{ kcal mol}^{-1}$ , which is negligible as compared to the error of more than  $0.05 \text{ kcal mol}^{-1}$  made in the test runs described below. We did not bin the  $s$  to evaluate the histogram  $N(s, t)$  in eq 18, but instead we used Gaussian functions of width  $0.01 \text{ rad}$ . This led to a smooth  $N(s, t)$  and a smooth free energy as shown in Figure 4A.

We then performed two different sets of simulations using the same  $\sigma$  for both dihedral angles. In one case,  $\sigma$  was smaller than the free-energy features ( $\sigma = 0.35 \text{ rad}$ ), in the other, larger ( $\sigma = 0.7 \text{ rad}$ ). Each set of simulations consisted of 100 WTMetaD runs of 20 ns each. The error relative to the reference free energy committed using the standard estimator of eq 3 and the new one in eq 18 was then compared.





**Figure 3.** Calculation of the average error for both GA (denoted with  $\sigma_G$ ) and DA (denoted with  $\tau_D$ ) schemes for alanine dipeptide as a function of time. The average error was calculated through a set of 100 runs and averaged every 120 ps. Two free-energy estimates are employed: the one of eq 18 denoted with  $\bar{F}_N$  and the one of eq 3 denoted with  $\bar{F}$ . The performance of eq 18 is always superior to that of eq 3, which is dramatically incorrect when DA or GA are employed. In the inset, it can be appreciated that the error scales linearly with  $1/\sqrt{t}$  as expected in WTMetaD. The use of eq 18 leads to the correct asymptotic behavior in contrast to eq 3.

From Figure 2, it can be seen that in all cases the new estimator produces consistent results and the expected asymptotic  $1/\sqrt{t}$  behavior. The old one works well for small Gaussians but in the case of the large ones is affected by a systematic error, due to the fact that it is not able to resolve the smaller features of the free energy landscape.

**4.2. Dynamically-Adapted Gaussians.** Having assessed the usefulness of eq 18, we turn to the evaluation of the performance of Gaussians of variable covariance using the DA scheme. This requires defining the parameter  $\tau_D$  that is a measure of the time required to sample two bins that we consider as different. In order to choose  $\tau_D$  in a manner which allows a fair comparison of constant and variable Gaussians covariance, we performed a preliminary 1 ns of standard

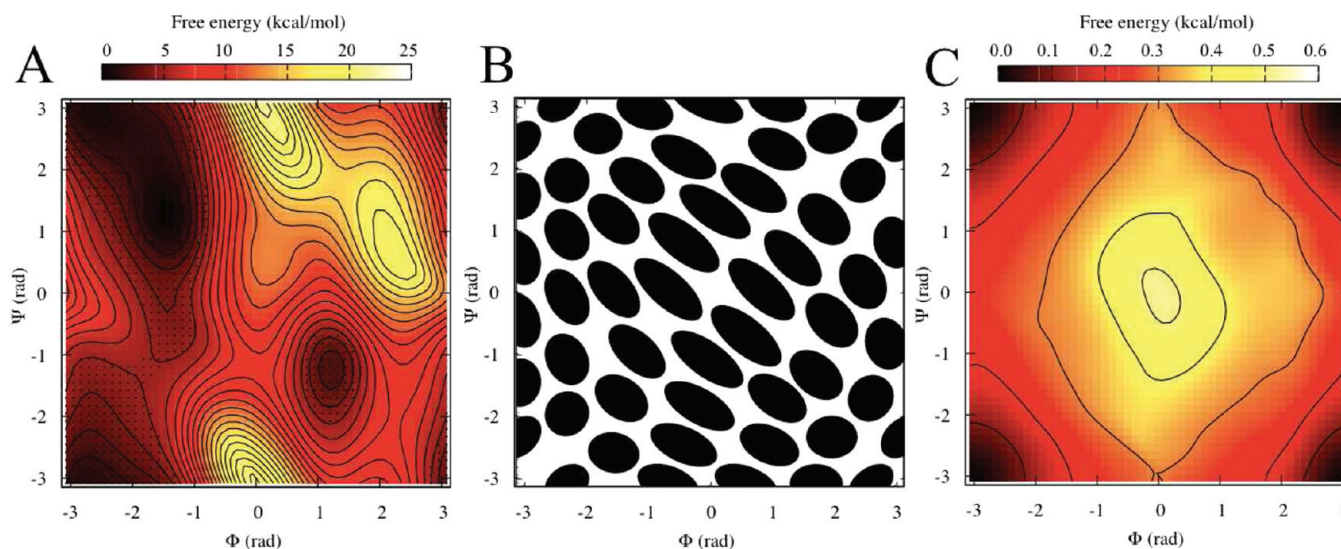
WTMetaD with Gaussians of a constant  $\sigma = 0.35$  rad width. We then tested different  $\tau_D$  values, and we chose the one that was able to fill on average the same volume deposited in the standard run. In this way, we ensured that the system was subject to a comparable filling rate. This gave the value  $\tau_D = 300$  fs. In analogy to the previous protocol, we performed 100 runs of 20 ns each and calculated the average error made in the region of the free-energy surface which is within lowest 5 kcal mol<sup>-1</sup> from the minimum of the reference surface.

The results are displayed in Figure 3, where the failure of the old estimator of eq 3 is evident. Instead, the new estimator gives correct results even when the covariance of the Gaussians is let to vary.

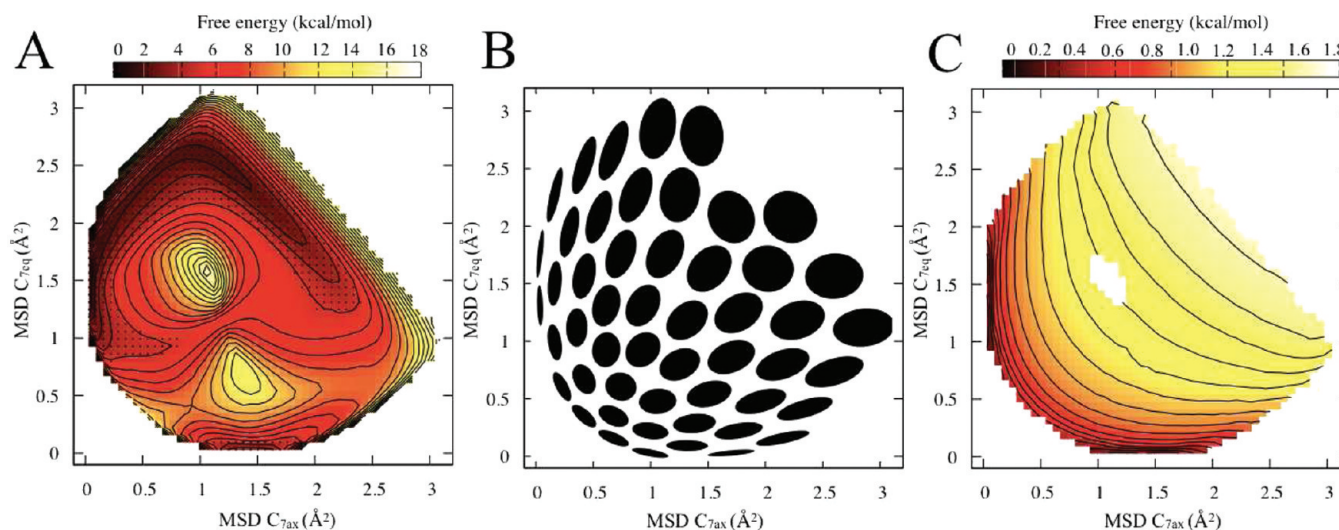
**4.3. Geometry-Adapted Gaussians: Ramachandran Plot.** We now turn to a test of the GA scheme for the same system using an identical protocol. The choice of a comparable  $\sigma_G$  was performed as before imposing the condition of the same volume filling rate with respect to a preliminary standard WTmetaD. This led to a value  $\sigma_G = 0.2$  Å. The results are again displayed in Figure 3. The free energy calculated through  $\bar{F}$  of eq 3 is expected to converge to the gauge invariant free-energy landscape, which is different from the standard one. Thus, even for long times, there is a systematic residual error. On the other hand, the new estimator does give the correct result, with a convergence rate which is very similar to that obtained with the standard calculation reported in Figure 2.

In Figure 4B, we give a pictorial view of the shape of the Gaussian potentials obtained by using the GA scheme. We also report in Figure 4C the correction due to the change in volume of the Gaussians, which measures the error made by using the old estimator. It can be seen that in this case the maximum error is as small as 0.6 kcal mol<sup>-1</sup>. However, this is by no means generally the case, as we shall see in the next section.

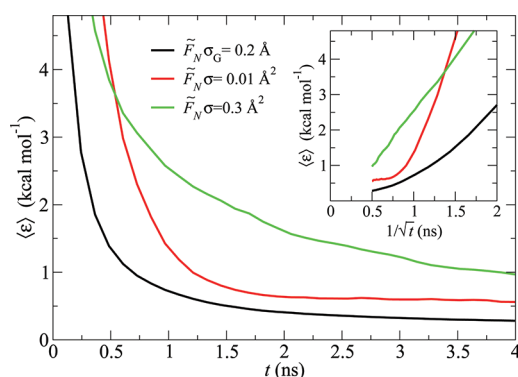
**4.4. Geometry-Adapted Gaussians: Double MSD.** We examine now the role that a different choice of collective variables might have on the error made by using the old estimator. While for the angle  $\Phi$  and  $\Psi$  the error was small, we



**Figure 4.** Panel A: Free-energy landscape on the two Ramachandran dihedral angles  $\Phi$  and  $\Psi$ . The dotted region represents the portion used for error calculations which lies within 5 kcal mol<sup>-1</sup> from the lowest free-energy point. Panel B: Representative sketch of the shape of the Gaussians produced on the Ramachandran plot for alanine dipeptide obtained by using the GA scheme of section 2.3. The size of each ellipse is scaled so to reflect the average size of the Gaussian potentials placed in each specific point. Panel C: Free-energy contribution coming from the change in volume of the Gaussians induced by the adoption of the GA scheme.



**Figure 5.** Panel A: Free-energy landscape on the MSD from the two metastable basins  $C_{7eq}$  and  $C_{7ax}$ . The dotted region represents the portion used for error calculations which lies within  $5 \text{ kcal mol}^{-1}$  from the lowest free energy point. Panel B: Representative sketch of the shape of the Gaussians produced by using two MSDs as CVs. The Gaussian widths were obtained by the GA scheme of section 2.3. The size of each ellipse is scaled so to reflect the average size of the Gaussian potentials placed in that specific point. Panel C: Free-energy contribution from the change in volume of the Gaussians induced by the adoption of the GA scheme. The blank region in the center is due to the lack of sampling for this simulation time.



**Figure 6.** WTMetaD for the double MSD case for alanine dipeptide in a vacuum. For each choice of  $\sigma$ , 100 runs of 4 ns each were performed, and the average error with respect to the reference free energy was calculated as function of time. Two different choices of  $\sigma$  are made and compared with the result obtained using the GA scheme with Gaussian width  $\sigma_G$ . The GA scheme is always superior and converges faster to the correct value.

expect it to be larger when dealing with CVs that are strongly nonlinear functions of the atomic coordinates. One such example is for instance CVs that measure the mean square deviation (MSD) from a reference structure or coordination functions that have sigmoidal dependence on the distance of two atoms or groups of atoms.

Thus, we studied once again alanine dipeptide in a vacuum and used as CVs the MSD from the two conformers  $C_{7eq}$  and  $C_{7ax}$  rather than the two torsional angles. The MSDs were calculated through optimal alignment by using Kearsley's algorithm,<sup>25</sup> and only the heavy atoms were considered in the metrics. In order to obtain reference values as accurate as possible rather than reweighting the configurations previously generated, we repeated the simulation with the same protocol as before. The result of this run, which also lasted  $1 \mu\text{s}$ , is shown in Figure 5A where it can be seen that in these new variables the free energy surface has two minima: one very narrow and the other wider.

By comparing Figures 5B and 4B, it is evident that the double MSD space induces a much larger change in shapes and volumes of the deposited Gaussian potentials. Correspondingly, the error made using the old estimator of eq 3 becomes larger (see Figure 5C). The benefit of using variable Gaussians becomes very apparent since we do not have to choose small Gaussians to resolve the narrow minima paying the price of a slow convergence, nor do we have to use larger Gaussians and sacrifice accuracy. This is exemplified in Figure 6, where we show the typical convergence behavior obtained by using the GA scheme of eq 12 and compare it to fixed- $\sigma$  runs, where  $\sigma$  was chosen to be appropriate either to the narrow minimum ( $\sigma = 0.01 \text{ Å}^2$ ) or to the larger one ( $\sigma = 0.3 \text{ Å}^2$ ). Using the new estimator, all three calculations appear to converge to the same limit, but with different rates. For narrow Gaussians ( $\sigma = 0.01 \text{ Å}^2$ ), the calculation converges to the right limit, albeit rather slowly. Similarly for very large Gaussians ( $\sigma = 0.3 \text{ Å}^2$ ), the convergence was very slow. When the GA scheme of section 2.3 is chosen, the asymptotic limit is reached faster and with a much smaller error.

## 5. DISCUSSION AND CONCLUSIONS

In summary, we have investigated in detail the possibility of performing metadynamics simulations where the repulsive Gaussian potentials have a width chosen on the fly and are not aligned with respect to the CVs. We have shown that using adaptive widths can lead to artifacts in the estimation of the free-energy landscape, which can be recovered by using a suitable estimator. Moreover, we have discussed two independent recipes to adapt the Gaussian shape, one based on the time evolution of the collective variables and another based on the intrinsic metrics of the microscopic coordinates. Both methods can be implemented using the same ingredients as standard metadynamics calculations, namely collective-variable values and first derivatives with respect to atomic positions. They are effective and have been shown to produce unbiased results on a standard benchmark. Additionally, they can remarkably improve the filling speed, especially when collective variables which are highly nonlinear functions of the

atomic positions are used. This is particularly helpful for MSD and MSD-based variables<sup>26</sup> or contact map-based variables, which are widely employed for systems of biological and condensed matter interest. For such variables, the usual choice of the Gaussian width fixed once and for all to the value of the CVs fluctuation measured in an initial unbiased run may in fact turn out to be suboptimal whenever the system is far from its initial configuration. In this respect, the gradient-adapted choice is of great help. These methods simplify the choice of the input parameters for a metadynamics simulation, significantly reducing the time which is usually spent in trial and errors. Both approaches can be used with CVs which are bounded, either by their intrinsic definition or by artificially added potentials. In the latter case, the version based on time evolution of the CVs might be more effective. Finally, they both can be straightforwardly combined with versions of MetaD which are based on multiple replicas.<sup>27–29</sup>

## APPENDIX A. BIAS DIVERGENCE LAW

The relation between the absolute free energy and the bias [eqs 2 and 17] contains a shift  $C(t)$  which does not depend on  $s$  but grows with the time. As already noted, this constant is irrelevant in the calculation of free-energy differences. However, it is instructive to compute explicitly its behavior in the long time limit. In the following, we shall do it in the small-width approximation, which is usually applied in the analysis of WTMetaD simulations. According to eq 14, the time derivative of the bias is

$$\dot{V}(s, t) = \frac{\omega e^{-V(s,t)/\Delta T} \sqrt{(2\pi)^d} \langle \det \sigma \rangle_s e^{-[F(s)+V(s,t)]/T}}{\int ds' e^{-[F(s')+V(s',t)]/T}} \quad (19)$$

As in the long time limit the bias grows uniformly in  $s$ , its time derivative is equal to the one of  $C(t)$ . By combining eq 19 and eq 15, one obtains

$$\begin{aligned} \dot{C}(t) &= \frac{\omega \sqrt{(2\pi)^d} e^{-C(t)/\Delta T}}{\int ds' \langle \det \sigma \rangle_s^{-\Delta T/(T+\Delta T)} e^{-F(s')/(T+\Delta T)}} \\ &\propto e^{-C(t)/\Delta T} \end{aligned} \quad (20)$$

By solving the differential equation eq 20, it can be seen that  $C(t)$  diverges logarithmically with time as

$$\lim_{t \rightarrow \infty} \frac{C(t)}{\Delta T \log t} = 1 \quad (21)$$

We underline that this is just the limiting behavior of  $C(t)$ . If its actual value is needed, for instance to align estimates of the free energy made at different times, the procedure illustrated in ref 30 could be used to estimate it. Note however that in ref 30 a different sign convention is used.

## APPENDIX B. SIMULATION DETAILS

In all the simulations shown, we employed alanine dipeptide (ACE–ALA–NME) in a vacuum as a model system, with molecular interactions described by the CHARMM27<sup>31</sup> force field. This system (see Figure 1) is a widely known benchmark for free-energy calculations.<sup>32–37</sup> Indeed, it displays two main basins, namely  $C_{7eq}$  and  $C_{7ax}$  separated by a sizable barrier of several  $k_B T$  at 300 K. A time step of 2 fs was employed, and all of the covalent bonds involving a hydrogen atom were constrained to the equilibrium distance by means of the

SHAKE<sup>38</sup> algorithm. A Langevin thermostat was used with a temperature of 300 K and a damping factor of 5 ps<sup>−1</sup>. The NAMD 2.8<sup>39</sup> molecular dynamics code was used and modified to add the adaptive shape WTMetaD capability.

## APPENDIX C. ERROR CALCULATION

Here, we describe the procedure adopted to evaluate the error between two free-energy landscapes for the numerical examples reported in the main text.

We first note that WTMetaD for finite  $\Delta T$  produces a more accurate histogram in low free-energy regions. Therefore, we selected a reference region in CVs space defined by those points lying within a value of  $\nu$  free-energy units with respect to the minimum of one of the free-energy surfaces, here termed reference free energy  $F_r(s)$ . In all of the calculations performed, the value of  $\nu$  was set to be 5 kcal mol<sup>−1</sup>.

In particular,  $F(s)$  being the free-energy surface whose error is required and  $s$  a point of the collective variables space, the error between the two surfaces is defined as

$$\epsilon = \sqrt{\frac{\int_S [\bar{F}_r(s) - \bar{F}(s)]^2 \theta(\nu - F_r(s)) ds}{\int_S \theta(\nu - F_r(s)) ds}} \quad (22)$$

Here,  $S$  is the multidimensional space in which the calculation is performed,  $\Phi$  and  $\Psi$  being for the Ramachandran plot, and  $\theta$  is a Heaviside step function. This equation amounts to calculating the average squared root difference between the two free energies  $\bar{F}_r(s)$  and  $\bar{F}(s)$  in the CVs space defined within  $\nu$  kcal mol<sup>−1</sup> from the minimum in the reference free energy  $\bar{F}_r(s)$ . The  $\bar{F}_r(s)$  is related to  $F_r(s)$  by a rigid shift of the free-energy surface with respect to the average value in the reference region:

$$\bar{F}_r(s) = F_r(s) - \frac{\int_S F_r(s) \theta(\nu - F_r(s)) ds}{\int_S \theta(\nu - F_r(s)) ds} \quad (23)$$

and a similar relation holds for the other free energy  $F(s)$  where, for consistency, the reference region is again defined on the reference free energy

$$\bar{F}(s) = F(s) - \frac{\int_S F(s) \theta(\nu - F_r(s)) ds}{\int_S \theta(\nu - F_r(s)) ds} \quad (24)$$

## ■ ASSOCIATED CONTENT

### Supporting Information

An illustrative example on a simple one-dimensional model is provided. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) Bolhuis, P.; Chandler, D.; Dellago, C.; Geissler, P. *Annu. Rev. Phys. Chem.* **2002**, *53*, 291–318.
- (2) Torrie, G. M.; Valleau, J. P. *J. Comput. Phys.* **1977**, *23*, 187–199.
- (3) Roux, B. *Comput. Phys. Commun.* **1995**, *91*, 275–282.
- (4) Huber, T.; Torda, A. E.; van Gunsteren, W. F. *J. Comput.-Aided Mol. Des.* **1994**, *8*, 695–708.
- (5) Wang, F.; Landau, D. P. *Phys. Rev. Lett.* **2001**, *86*, 2050–2053.
- (6) Darve, E.; Pohorille, A. *J. Chem. Phys.* **2001**, *115*, 9169–9183.
- (7) Laio, A.; Parrinello, M. *Proc. Natl. Acad. Sci. U. S. A.* **2002**, *99*, 12562–12566.
- (8) Laio, A.; Rodriguez-Forteza, A.; Gervasio, F. L.; Ceccarelli, M.; Parrinello, M. *J. Phys. Chem. B* **2005**, *109*, 6714–6721.
- (9) Bussi, G.; Laio, A.; Parrinello, M. *Phys. Rev. Lett.* **2006**, *96*, 090601.
- (10) Barducci, A.; Bonomi, M.; Parrinello, M. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2011**, *1*, 826–843.
- (11) Marsili, S.; Barducci, A.; Chelli, R.; Procacci, P.; Schettino, V. *J. Phys. Chem. B* **2006**, *110*, 14011–14013.
- (12) Barducci, A.; Bussi, G.; Parrinello, M. *Phys. Rev. Lett.* **2008**, *100*, 020603.
- (13) Iannuzzi, M.; Laio, A.; Parrinello, M. *Phys. Rev. Lett.* **2003**, *90*, 238302.
- (14) CPMD; IBM Corp: Armonk, NY, 1990–2008; MPI für Festkörperforschung Stuttgart: Stuttgart, Germany, 1997–2000. <http://www.cpmc.org/> (accessed May 2012).
- (15) Tribello, G. A.; Ceriotti, M.; Parrinello, M. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 17509–17414.
- (16) Martoňák, R.; Donadio, D.; Oganov, A.; Parrinello, M. *Nat. Mater.* **2006**, *5*, 623–6.
- (17) Martoňák, R.; Donadio, D.; Oganov, A.; Parrinello, M. *Phys. Rev. B* **2007**, *76*, 14120.
- (18) Best, R.; Hummer, G. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 1088.
- (19) Vanden-Eijnden, E. In *Multiscale, Modelling, and Simulation*; Attinger, S., Koumoutsakos, P., Eds.; Springer: Berlin, 2004; p 3568.
- (20) Vanden-Eijnden, E.; Tal, F. *J. Chem. Phys.* **2005**, *123*, 184103.
- (21) Hartmann, C.; Schütte, C. *Phys. D* **2007**, *228*, 59–63.
- (22) Singh, S.; Chiu, C.; de Pablo, J. *J. Stat. Phys.* **2011**, *145*, 932–945.
- (23) Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graphics* **1996**, *14*, 33–38.
- (24) Ramachandran, G. N.; Ramakrishnan, C.; Sasisekharan, V. *J. Mol. Biol.* **1963**, *7*, 95.
- (25) Kearsley, S. K. *Acta Crystallogr., Sect. A* **1989**, *45*, 208–210.
- (26) Branduardi, D.; Gervasio, F. L.; Parrinello, M. *J. Chem. Phys.* **2007**, *126*, 054103.
- (27) Raiteri, P.; Laio, A.; Gervasio, F. L.; Micheletti, C.; Parrinello, M. *J. Phys. Chem. B* **2006**, *110*, 3533–3539.
- (28) Bussi, G.; Gervasio, F. L.; Laio, A.; Parrinello, M. *J. Am. Chem. Soc.* **2006**, *128*, 13435–13441.
- (29) Piana, S.; Laio, A. *J. Phys. Chem. B* **2007**, *111*, 4553–4559.
- (30) Bonomi, M.; Barducci, A.; Parrinello, M. *J. Comput. Chem.* **2009**, *30*, 1615–1621.
- (31) MacKerell, A. D., Jr.; et al. *J. Phys. Chem. B* **1998**, *102*, 3586–3616.
- (32) Maragliano, L.; Fischer, A.; Vanden-Eijnden, E. *J. Chem. Phys.* **2006**, *125*, 024106.
- (33) Lazaridis, T.; Tobias, D. J.; Brooks, C.; Paulaitis, M. E. *J. Chem. Phys.* **1991**, *95*, 7612–7625.
- (34) Tobias, D. J.; Brooks, C. L. *J. Phys. Chem.* **1992**, *96*, 3864–3870.
- (35) Bartels, C.; Karplus, M. *J. Comput. Chem.* **1997**, *18*, 1450–1462.
- (36) Apostolakis, J.; Ferrara, P.; Caflisch, A. *J. Chem. Phys.* **1999**, *110*, 2099–2108.
- (37) Smith, P. E. *J. Chem. Phys.* **1999**, *111*, 5568–5579.
- (38) Ryckaert, J. P.; Ciccotti, G.; Berendsen, H. J. C. *J. Comput. Phys.* **1977**, *23*, 327–341.
- (39) Phillips, J. C.; Braun, R.; Wang, W.; Gumbart, J.; Tajkhorshid, E.; Villa, E.; Chipot, C.; Skeel, R. D.; Kalé, L.; Schulten, K. *J. Comput. Chem.* **2005**, *26*, 1781–802.