Employing Sampling Entropy in Repository Based Adaptive Umbrella Sampling

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(June 26, 2009)

Abstract

To determine free energy surfaces along chosen reaction coordinates is a common and important task in simulating complex systems. Due to the complexity of energy landscape and the existence of high barriers, one widely pursued direction to develop efficient simulation methods is to achieve uniform sampling among thermodynamic states of interest. In this work, we have demonstrated sampling entropy (SE) as an excellent indicator for uniform sampling as well as for the convergence of free energy simulations. By introducing sampling entropy and concentration theorem into the biasing potential updating scheme, we have significantly improved the adaptivity, robustness and applicability of our recently developed Repository Based Adaptive Umbrella Sampling (RBAUS) approach [*J. Chem. Phys.*, **128**, 204106 (2008)]. Besides simulations of one dimensional free energy profile for various systems, the generality and efficiency of this new RBAUS-SE approach has been further demonstrated in determining two dimensional free energy surfaces of alanine dipeptide in gas phase as well as in water.

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I. INTRODUCTION

Determination of free energy surfaces with computer simulations is of critical importance in quantitatively elucidating many chemical and biological processes, including conformational changes, molecular recognition and chemical reactions. Besides challenges regarding accuracy of the potential energy surface and its computational efficiency, another key obstacle is to achieve adequate sampling of the configuration space of interest. Due to the complexity of energy landscape and the existence of high barriers, transitions among distinct thermodynamic states of significance are rare events, which constitute sampling bottlenecks in a straightforward application of molecular dynamics or Monte Carlo simulations. A widely employed strategy to overcome this difficulty is the introduction of an external biasing potential into the Hamiltonian which forces the system to visit the high barrier regions[1–10].

An ideal choice of the biasing potential would be the negative of the free energy surfaces so that uniform sampling along chosen reaction coordinates can be achieved. Unfortunately, such info is exactly what we try to obtain from simulations and is not known in the first place. In past years, many adaptive sampling approaches[3,8,11–27] have been proposed to overcome this inherent challenge. Among them, very recently we have introduced the Repository Based Adaptive Umbrella Sampling (RBAUS) method[27], in which a sampling repository is periodically updated based on the latest simulation data, and the accumulated knowledge and sampling history is then employed to determine whether and how to update the biasing umbrella potential to achieve more uniform sampling for subsequent simulations. In comparison with other adaptive sampling methods, a unique and attractive feature of the RBAUS method is that the frequency for updating the biasing potential is not predetermined, but depends on the sampling history and is adaptively determined on-the-fly, which smoothly bridges nonequilibrium and equilibrium simulations. Such an adaptive updating is achieved by employing the following general principle: the biasing potential needs to be updated if the subsequent simulations still explores the previously oversampled region more than the previously undervisited; on the other hand, the biasing potential update is not needed if the subsequent simulations is achieving more uniform sampling. Thus we can see that

a key element of the the RBAUS approach is the determination of sampling uniformity. In addition, a well-defined measure of sampling uniformity can also be used to check the convergence of determined free energy surfaces.

In this work, we have demonstrated sampling entropy (SE) as an excellent indicator for uniform sampling as well as for the convergence of free energy simulations. By introducing sampling entropy into the biasing potential updating scheme, the adaptivity, robustness and applicability of the RBAUS approach have been significantly improved, including the determination of two dimensional free energy surfaces.

II. THEORY AND METHOD

This section is organized as follows. First a brief review of the RBAUS method is given, then the rational of employing sampling entropy and entropy concentration theorem in adaptive sampling are presented, and finally the resulted RBAUS-SE approach is described.

A. Review of Repository Based Adaptive Umbrella Sampling (RBAUS)

In umbrella sampling[2,24,27] with a biased Hamiltonian H_b,

$$\mathrm{H_b} = \mathrm{H}_0 + \mathrm{V_b}(\eta(\mathbf{R})), \tag{1}$$

the free energy surface along predefined reaction coordinates $\eta(\mathbf{R})$ can be computed as

$$A(\eta) = -k_B T \ln \frac{\mathrm{NS}(\eta)\mathrm{e}^{\mathrm{V_b}(\eta)/k_B T}}{\int \mathrm{d}\eta \mathrm{NS}(\eta)\mathrm{e}^{\mathrm{V_b}(\eta)/k_B T}} + c \tag{2}$$

where $\mathrm{NS}(\eta)$ as the number of configurations with given reaction coordinates η in the canonical ensemble generated with the biased Hamiltonian $\mathrm{H_b}$, and c can be any constant. Thus for a given biased ensemble, $\mathrm{NS}(\eta)$ is the raw sampling number of η, and $\mathrm{K}(\eta) = \mathrm{N_b}(\eta)\mathrm{e}^{\mathrm{V_b}(\eta)/k_B T}$ can be considered as the corresponding unbiased knowledge of η from this biased simulation.

In numerical simulations, it is a common practice to divide reaction coordinates η into Z bins. For the RBAUS approach[27], the sampling repository stores and updates mainly two kinds of information: the accumulated unbiased knowledge K[i] and the accumulated raw sampling number NS[i] for each bin [i]. K[i] is employed to determine the biasing potential with the following formula:

$$\mathrm{A[i]} = k_B T \ln \frac{\mathrm{K[i]} * \mathrm{Z}}{\sum_{\mathrm{i}=1}^{\mathrm{Z}} \mathrm{K[i]}}, \tag{3}$$

Meanwhile, NS[i] is used to compute the "histmax-histmin ratio" (HHR), the ratio of its largest value of NS[i] to its lowest value, which is then employed to determine whether to update the biasing potential. However, the HHR is not a global uniform sampling indicator, and is not defined before all bins are visited. In our original RBAUS approach, several empirical parameters need to be carefully chosen to result in an efficient heuristic scheme to determine one dimensional free energy profiles. Although tests on several very different systems with barriers ranging from 3 to 30 kcal/mol have been successful, the scheme becomes inefficient when being applied to determine two-dimensional free energy surfaces. The problem mainly comes from the inadequacy of HHR as a uniform sampling indicator when the dimension of reaction coordinates and the number of bins increase. Meanwhile, the correlation between HHR and the convergence in determining 1-D free energy profiles for those different test systems is quite weak, and no general criteria to stop the RBAUS simulations can be suggested. Thus, we are motivated to find a better uniform sampling indicator than HHR so that the robustness, adaptivity and efficiency of the RBAUS approach can be further significantly improved.

B. Sampling Entropy, Concentration Theorem and Uniform Sampling

Given Z bins along chosen reaction coordinates, the sampling entropy[28,29] is defined as

$$\mathrm{SE} = -\sum_{\mathrm{i}=1}^{\mathrm{Z}} \frac{\mathrm{NS[i]}}{\mathrm{NS_{total}}} \ln \frac{\mathrm{NS[i]}}{\mathrm{NS_{total}}} \tag{4}$$

where NS[i] is the number of times that the *i*th bin has been visited and $\mathrm{NS_{total}} = \sum_{\mathrm{i=1}}^{\mathrm{Z}} \mathrm{NS[i]}$. We can see that if only one bin is visited, the sampling entropy has the minimum value of zero; the SE increases with more bins sampled, and it has the maximum value of lnZ if all bins have been equally sampled. Thus the normalized sampling entropy, $NSE = \frac{SE}{lnZ}$, which ranges from 0 to 1, would serve as a general uniform sampling indicator independent of the number of bins. It is dependent on sampling data of all bins and is very well-defined even when bins are not sampled. Thus, two main deficiencies of HHR have been avoided when using normalized sampling entropy as a uniform sampling indicator.

For complex systems, even with flat free energy surfaces along reaction coordinates of interest, to achieve uniform sampling with molecular dynamics simulations requires the simulation time to be sufficiently long. At the initial period of simulation, the value of uniform sampling entropy would be expected to be much less than 1 regardless of its underlying free energy landscape. Here comes entropy concentration theorem (ECT) by Jaynes[28]: Given Z number of bins with equal probability and N independent sampling points, there is probability of P that the resulted sampling entropy SE(Z,N) should be in the range of

$$lnZ - \frac{\chi^2_{\text{Z-1}}(1-P)}{2N} \leq SE(Z,N) \leq lnZ, \tag{5}$$

where $\chi^2_{\text{Z-1}}(1-P)$ denotes the critical chi-squared for Z-1 degrees of freedom at the 100(1-P) percent significance level. Here by defining the ECT factor

$$ECT(Z,N) = lnZ - \frac{\chi^2_{\text{Z-1}}(1-P)}{2N}, \tag{6}$$

which provides continuing guidance regarding the expectation value of the sampling entropy with increasing independent sampling number N. This would form the theoretical basis to decide whether to update the biasing potential in adaptive sampling. Typically, the conventional 5-percent significance level can be employed, such as: $\chi^2_{49}(0.05) = 66.34$, $\chi^2_{5183}(0.05) = 5351.60$. The quantiles of chi-square distribution could be easily obtained by the function "qchisq" in R language[30].

C. Sampling Entropy based RBAUS Approach

By employing sampling entropy and concentration theorem in biasing potential updating scheme, the recently developed Repository Based Adaptive Umbrella Sampling (RBAUS) approach has been further improved. The resulted RBAUS-SE simulation scheme is presented in detail below:

- **STEP 0: Initial Repository Setup.** Given Z bins along chosen reaction coordinates, this is to set initial values of K[i] and NS[i] for all bins.

- **STEP 1: Biasing Potential Update.** With the accumulated unbiased knowledge K[i], the free energy profile A[i] is calculated with the following equation:

$$\mathrm{A[i]} = -k_B T \ln \frac{\mathrm{K[i]} * \mathrm{Z}}{\sum_{\mathrm{i}=1}^{\mathrm{Z}} \mathrm{K[i]}} \tag{7}$$

  The biased potential $\mathrm{V_b}$ is then obtained based on the negative of the calculated free energy profile. It should be noted that with Eq. 7, A[i] would be zero when K[i] is equal to the average of the accumulated knowledge among all bins - a desired property for constructing the biased potential.

- **STEP 2: Biased Simulations.** Perform molecular dynamics simulations with the biased Hamiltonian $\mathrm{H_0} + \mathrm{V_b}$ and collect the raw histogram h[i], which is the number of sampled configurations in each bin.

- **STEP 3: Repository Update.**

$$\mathrm{NS[i]} = \mathrm{NS[i]} + \mathrm{h[i]} \tag{8}$$

$$\mathrm{K[i]} = \mathrm{K[i]} + \mathrm{h[i]} \mathrm{e}^{\mathrm{V_b[i]}/k_B T} \tag{9}$$

  The updated K[i] would be employed to calculate the current estimation of the free energy profile A[i] through Eq.7 if desired. At the same time, from the accumulated raw sampling

number NS[i], the sampling entropy and the ECT factor ECT(Z,N) are calculated with Eq. 4 and Eq. 6, respectively. It should be noted that even if free energy surface is flat, sampling among all bins would be far from random in MD simulations. Thus the value of N in Eq. 6 should be proportional to $\mathrm{NS_{total}} = \sum_{\mathrm{i}=1}^{\mathrm{Z}} \mathrm{NS[i]}$, but be much less than that. To take this into account, the value of N in Eq. 6 is obtained from scaling $\mathrm{NS_{total}}$ by a pre-determined factor C: $N = \frac{NS_{total}}{C}$. Throughout this work, we have chosen C to be 100.

- **STEP 4: Decision Make on whether to update the biasing potential.** If the calculated NSE is larger than 0.99 or the SE is larger than the ECT factor ECT(Z,N), the biasing potential update is not needed, goto Step 2. Otherwise, update is needed, goto Step 5.

- **STEP 5: Repository Consolidation.** Here the accumulated unbiased knowledge in the sampling repository is consolidated by setting: $K[i] = K[i] * \frac{e^{SE}}{e^{ECT(Z,N)}}$ when NSE is less than 0.98 . Go to STEP 1.

The above scheme is summarized into a flow chart shown in Fig.2, which keeps the same structure with the original RBAUS approach[27] but employs sampling entropy in STEP 4 and 5. It should be noted that 1.0 is the theoretical NSE for the ideal uniform sampling, and the ECT(K,N) provides a guidance regarding the expectation value of the sampling entropy with the independent sampling number N. Thus in STEP 4, when NSE is larger than 0.99 or SE is larger than ECT(K,N), the current biasing potential can be considered to be good enough and thus no update is needed. In STEP 5, the employment of $\frac{e^{SE}}{e^{ECT(Z,N)}}$ as the scaling factor rather than a fixed value of 0.618 in the original RBAUS scheme makes the repository consolidation step more adaptive based on the current knowledge about uniform sampling. Overall, the resulted RBAUS-SE approach is more robust and general than the original one, which will be further demonstrated by test results below. It should be also noted that the embarrassingly parallel simulations can be very easily implemented in the RBAUS-SE Method as in the original one.

III. IMPLEMENTATION AND COMPUTATIONAL DETAIL

We have implemented the above presented RBAUS-SE simulation scheme in the TINKER4.2 suite of molecular simulation program[31]. The 1-D biasing potential is described with the shape-preserving smoothing spline by using Renka's TSPACK (one-dimension) package[32], and 2-D biasing potential is represented by employing the surface interpolation package SRFPACK[33] in conjunction with TRIPACK[34]. First we tested the implemented scheme to determine 1-D potential of mean force (PMF) for two systems that we have examined previously[27]: one is a simple system which contains two particles interacting with a double well potential having a barrier of 24 kcal/mol, and the other is the Na^+ and Cl^- ion pair association in water. For both systems, simulations with four replicas have been carried out, and the repository is updated every 1000 data points collected. To check the convergence of simulations, we have calculated the root-mean-square deviation (RMSD) of the simulated PMF with respect to the reference one computed from umbrella sampling:

$$\mathrm{RMSD} = \sqrt{\frac{\sum_{\mathrm{i}=1}^{\mathrm{Z}} [\mathrm{PMF}_{sim}[\mathrm{i}] - \mathrm{PMF}_{ref}[\mathrm{i}]]^2}{\mathrm{Z}}} \tag{10}$$

It should be noted that in these two cases, the distance of two particles r is chosen as the reaction coordinate. Thus the potential of mean force PMF(r) is related to the free energy profile (A(r)) as: $PMF(r) = A(r) + 2k_BT \ln r$. To further demonstrating the applicability and performance the RBAUS-SE approach, we have employed it to determine 2-D free energy surfaces of the alanine peptide in gas phace and in aqueous solution as a function of the backbone dihedral angle ϕ and ψ, as illustrated in Fig. 1. This has become a classical example to test enhanced sampling approaches[35–37,20,38,24,26,39]. In our simulations, the alanine dipeptide and water molecules are described by the CHARMM27 force field[40]. For the aqueous phase, the simulation of one alanine dipeptide molecule and 245 TIP3P water[41] molecules is performed in the cubic box of 19.7429 $\AA$ with periodic boundary conditions. The cutoff distance of 9$\AA$ has been used for the wan der Waals and electrostatic interactions. The simulations are based on 1 fs time step and 300K temperature. For the RBAUS-SE simulations, 24 replicas have been employed with time step of 1 fs and temperature of 300 K. The bin width along reaction coordinates (ϕ and ψ) is set to be 5 degree, and the

repository has been updated every 1200 collecting data point. The reference FES for each phase is calculated from 24 replica equilibrium MD simulations with a fixed biasing potential. 6 ns simulations has run for each replica. The biased potential employed for the equilibrium simulations is obtained from the converged RBAUS-SE simulations.

In all our test cases, we have assumed no prior knowledge of the system, and set all initial K[i] to be 1. In an ideal situation with flat free energy surface, the diffusion rate along reaction coordinates would be inverse proportional to the square root of reduced mass of atoms involved. With this as the guidance, the frequency to collect data has been set to be 1fs, 5fs and 2 fs respectively for the double well system (each particle has a mass of 1 amu), NaCl, and alanine peptide.

IV. RESULTS AND DISCUSSION

We have applied the RBAUS-SE method to the double well potential model with the barrier of 24 kcal/mol and the dissociation of a NaCl molecule in water. The results are shown in Fig. 3 and 4. Although its overall simulation efficiency is found to be very similar to the original RBAUS scheme[27] in determining such 1-D PMFs, one attractive advantage of the RBAUS-SE approach is that we can monitor the simulation progress through measuring the normalized sampling entropy (NSE). As expected, the error in the simulated PMF decreases with the increase of the NSE. When the NSE first reaches 0.99, the error in the simulated PMF is about 0.1 kcal/mol for the double well system and 0.2 kcal/mol for NaCl in aqueous solution, both of which are below 0.5 kT (about 0.3 kcal/mol when T = 300 K). Meanwhile, the plotted normalized ECT and NSE curves also illustrate how such information has been employed to determine whether to update the biasing potential. We can see that for both systems, initially these are non-equilibrium simulations, and there is no biasing potential updating after about 65 ps for the double well system and after about 250 ps for the NaCl system.

To further demonstrating the robustness, efficiency and generality of the RBAUS-SE method, it has been employed to determine 2-D free energy surfaces of the alanine dipeptide in vacuum and water. Fig. 6 and 7 illustrate the calculated FES contour maps at different simulation times

(10ps, 50ps, 100ps, 500ps) for the alanine dipeptide in vacuum and aqueous solution respectively. For each case, it only takes about 50ps simulation for each replica to obtain some general features of the 2D free energy surface, and the the FES at 500 ps is in excellent agreement with the corresponding reference FES in Figure 5. The RMSD curves of calculated FES as well as NSE and normalized ECT curves are shown in Figure 8 and 9, which show that with the progress of simulations, the NSE increases and the biasing-potential update stops at about 0.25 ns for both gas phase and aqueous phase. Those figures also indicate that when the NSE first reaches 0.99, the error in calculated FES is a little less than 0.3 kcal/mol for the alanine dipeptide in vacuum and about 0.2 kcal/mol for the alanine dipeptide in aqueous solution. These results indicate that the RBAUS-SE approach is an efficient approach to determine converged 2-D free energy surfaces.

Figure 10 and 11 show the correlation between the error in simulated free energy surfaces and the normalized sampling entropy (NSE) in both RBAUS-SE simulations and equilibrium MD simulations without free energy barriers along reaction coordinates of interest for all four test systems. These results clearly demonstrate that the normalized sampling entropy is an excellent indicator for the convergence of free energy simulations as well as for the uniform sampling. Based on these results, a criteria to stop RBAUS-SE simulations can be suggested, such as NSE=0.993. For all of our four test systems, the error is no more than 0.2 kcal/mol when NSE=0.993.

V. CONCLUSION

In this work, by employing normalized sampling entropy and concentration theorem, we have further improved the adaptivity, robustness and applicability of the RBAUS approach. The tests on alanine peptide in gas phace as well as in water indicate that the RBAUS-SE approach is an efficient approach to determine converged 2-D free energy surfaces. Our results clearly demonstrate that the normalized sampling entropy is an excellent indicator for the convergence of free energy simulations as well as for the uniform sampling, which should also be useful in further improving other adaptive sampling methods.

VI. ACKNOWLEDGMENTS

This work has been supported by the National Science Foundation (CHE-CAREER-0448156) and National Institute of Health (R01-GM079223). We appreciate the computational resources and support provided by NYU-ITS.

REFERENCES

[1] C. Chipot and A. Pohorille, *Free Energy Calculations: Theory and Applications in Chemistry and Biology* (Spring, 2007).

[2] G. N. Patey and J. P. Valleau, J. Chem. Phys. **63**, 2334 (1975).

[3] M. Mezei, J. Comput. Phys. **68**, 237 (1987).

[4] B. Roux, Comput. Phys. Commun. **91**, 275 (1995).

[5] H. Grubmuller, Phys. Rev. E **52**, 2893 (1995).

[6] A. F. Voter, Phys. Rev. Lett. **78**, 3908 (1997).

[7] C. Jarzynski, Phys. Rev. E **56**, 5018 (1997).

[8] A. Laio and M. Parrinello, Proc. Natl. Acad. Sci. U. S. A. **99**, 12562 (2002).

[9] J. A. Rahman and J. C. Tully, J. Chem. Phys. **116**, 8750 (2002).

[10] D. Hamelberg, J. Mongan, and J. A. Mccammon, J. Chem. Phys. **120**, 11919 (2004).

[11] C. Bartels and M. Karplus, J. Comput. Chem. **18**, 1450 (1997).

[12] C. Bartels, M. Schaefer, and M. Karplus, J. Chem. Phys. **111**, 8048 (1999).

[13] R. Rajamani, K. J. Naidoo, and J. L. Gao, J. Comput. Chem. **24**, 1775 (2003).

[14] J. Wang, Y. Gu, and H. Y. Liu, J. Chem. Phys. **125**, 094907 (2006).

[15] F. Calvo, Mol. Phys. **100**, 3421 (2002).

[16] F. G. Wang and D. P. Landau, Phys. Rev. E **64**, 056101 (2001).

[17] E. Darve and A. Pohorille, J. Chem. Phys. **115**, 9169 (2001).

[18] J. Henin and C. Chipot, J. Chem. Phys. **121**, 2904 (2004).

[19] G. Bussi, A. Laio, and M. Parrinello, Phys. Rev. Lett. **96**, 090601 (2006).

[20] B. Ensing, M. De vivo, Z. W. Liu, P. Moore, and M. L. Klein, Accounts Chem. Res. **39**, 73 (2006).

[21] H. Li, D. Min, Y. Liu, and W. Yang, J. Chem. Phys. **127**, 094101 (2007).

[22] A. Laio and F. L. Gervasio, Rep. Prog. Phys. **71**, 126601 (2008).

[23] T. Lelievre, M. Rousset, and G. Stoltz, J. Chem. Phys. **126**, 134111 (2007).

[24] S. Marsili, A. Barducci, R. Chelli, P. Procacci, and V. Schettino, J. Phys. Chem. B **110**, 14011 (2006).

[25] A. Barducci, G. Bussi, and M. Parrinello, Phys. Rev. Lett. **100**, 020603 (2008).

[26] L. Q. Zheng and W. Yang, J. Chem. Phys. **129**, 014105 (2008).

[27] H. Zheng and Y. Zhang, J. Chem. Phys. **128**, 204106 (2008).

[28] E. T. Jaynes, Proc. IEEE **70**, 939 (1982).

[29] S. Park and V. S. Pande, Phys. Rev. E **76**, 016703 (2007).

[30] R. D. C. Team, *R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing* (2006).

[31] J. W. Ponder, *TINKER, Software Tools for Molecular Design, Version 4.2* (PUBLISHER, The most updated version for the TINKER program can be obtained from J. W. Ponder's World Wide Web site at http://dasher.wustl.edu/tinker., Jun. 2004).

[32] R. J. Renka, ACM Trans. Math. Softw. **19**, 81 (1993).

[33] R. J. Renka, ACM Trans. Math. Softw. **22**, 9 (1996).

[34] R. J. Renka, ACM Trans. Math. Softw. **22**, 9 (1996).

[35] D. J. Tobias and C. L. Brooks, J. Phys. Chem. **96**, 3864 (1992).

[36] P. E. Smith, J. Chem. Phys. **111**, 5568 (1999).

[37] L. Rosso, J. B. Abrams, and M. E. Tuckerman, J. Phys. Chem. B **109**, 4162 (2005).

[38] C. A. F. De oliveira, D. Hamelberg, and J. A. Mccammon, J. Chem. Phys. **127**, 175105 (2007).

[39] J. Apostolakis, P. Ferrara, and A. Caflisch, J. Chem. Phys. **110**, 2099 (1999).

[40] A. D. Mackerell *et al.*, J. Phys. Chem. B **102**, 3586 (1998).

[41] W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. W. Impey, and M. L. Klein, J. Chem. Phys. **79**, 926 (1983).

FIGURES

FIG. 1. Schematic of the alanine dipeptide showing the ϕ and ψ angles

FIG. 2. The fbw chart for the repository based adaptive umbrella sampling approach.

FIG. 3. The RMSD, normalized sampling entropy (NSE) and normalized ECT factor (NECT) curves for the double-well model system with a barrier of 24 kcal/mol . The circle symbols represent the biasing-potential-updating points.

FIG. 4. The RMSD, normalized sampling entropy (NSE) and normalized ECT factor (NECT) curves for the dissociation of a sodium chloride ion-pair in aqueous solution. The circle symbols represent the biasing-potential-updating points.

FIG. 5. The reference free energy surfaces of the alanine dipeptide system as a function of ϕ and ψ torsional angles in gas phase(left graph) and in aqueous phase(right graph) by biasing equilibrium umbrella sampling for 1ns with 24 replica.

FIG. 6. Free energy surfaces of the alanine dipeptide system as a function of ϕ and ψ torsional angles in gas phase with 1 kal/mol contour interval calculated by RBAUS-SE with 24 replica. Upper left: the free energy surface obtained after 10 ps simulation; Upper right: the free energy surface obtained after 50 ps simulation; Lower left: the free energy surface obtained after 100 ps simulation; Lower right: the free energy surface obtained after 500 ps simulation.

FIG. 7. Free energy surfaces of the alanine dipeptide system as a function of ϕ and ψ torsional angles in aqueous phase with 1 kal/mol contour interval calculated by RBAUS-SE with 24 replica. Upper left: the free energy surface obtained after 10 ps simulation; Upper right: the free energy surface obtained after 50 ps simulation; Lower left: the free energy surface obtained after 100 ps simulation; Lower right: the free energy surface obtained after 500 ps simulation.

FIG. 8. The RMSD, normalized sampling entropy (NSE) and normalized ECT factor (NECT) curves for the alanine dipeptide in gas phase. The circle symbols represent the biasing-potential-updating points.

FIG. 9. The RMSD, normalized sampling entropy (NSE) and normalized ECT factor (NECT) curves for the alanine dipeptide in aqueous phase. The circle symbols represent the biasing-potential-updating points.

FIG. 10. The correlation of the RMSD and Sampling Entropy for all the systems based on RBAUS-SE calculations

FIG. 11. The correlation of the RMSD and Sampling Entropy for all the systems with flat free energy profiles based on equilibrium MD calculations

Figure 1: H. Zheng and Y. Zhang

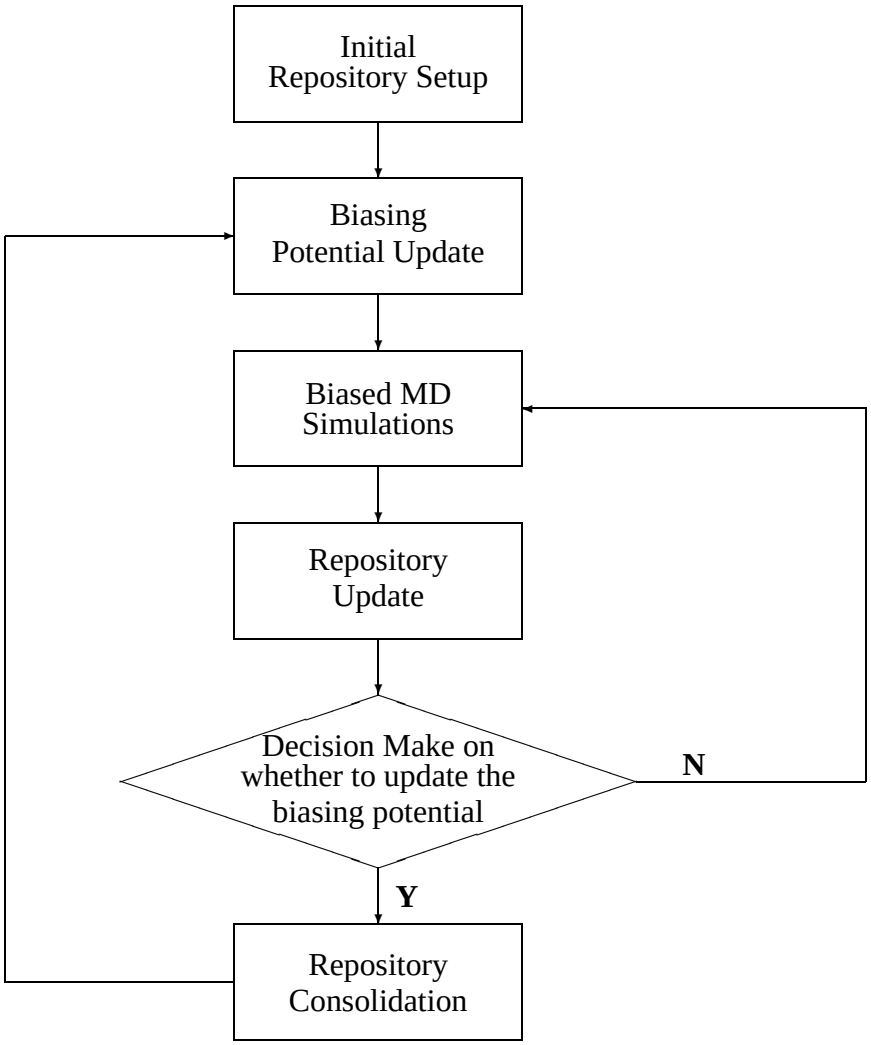
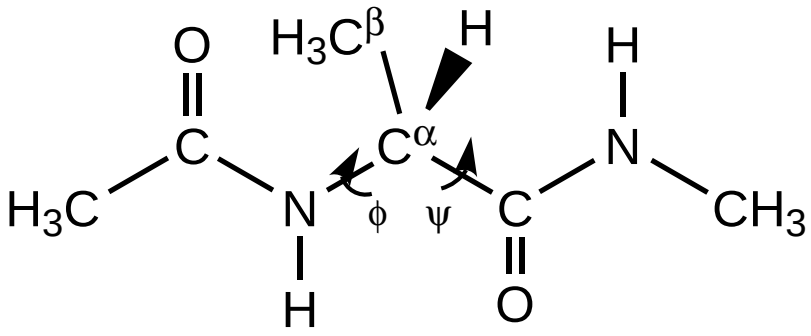


Figure 1: H.Zheng and Y. Zhang



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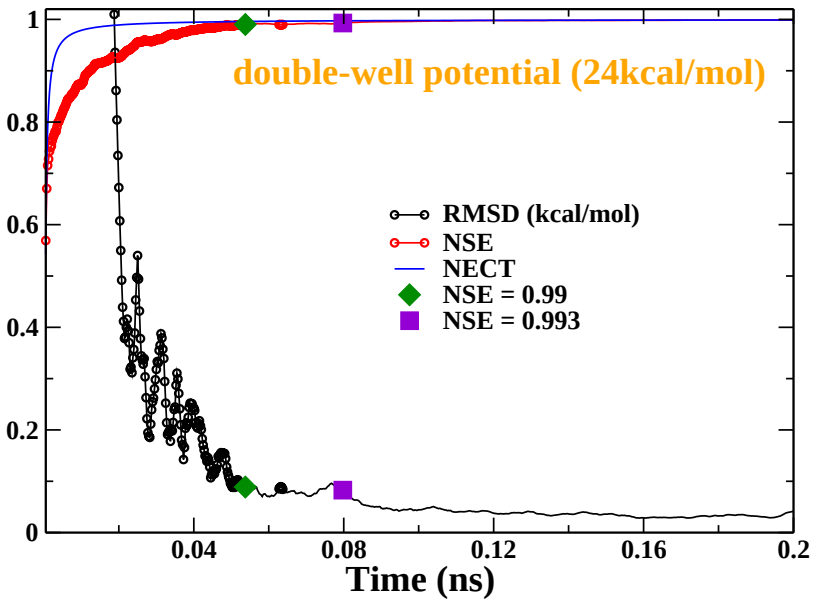

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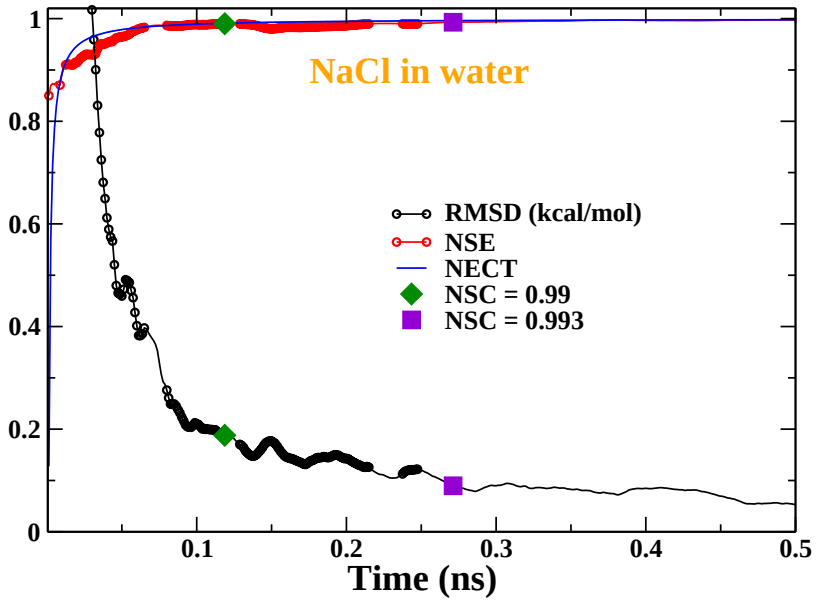

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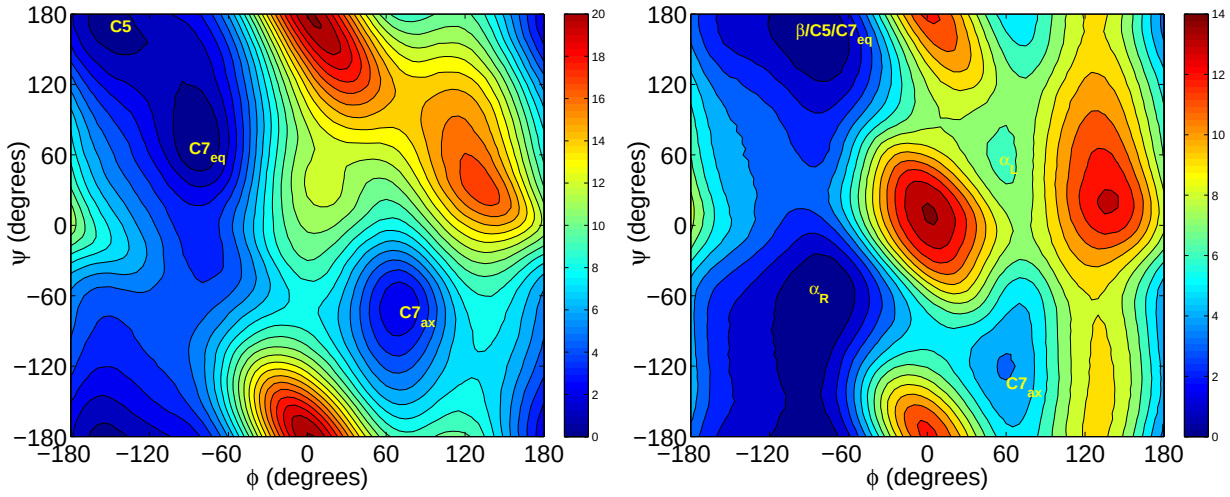

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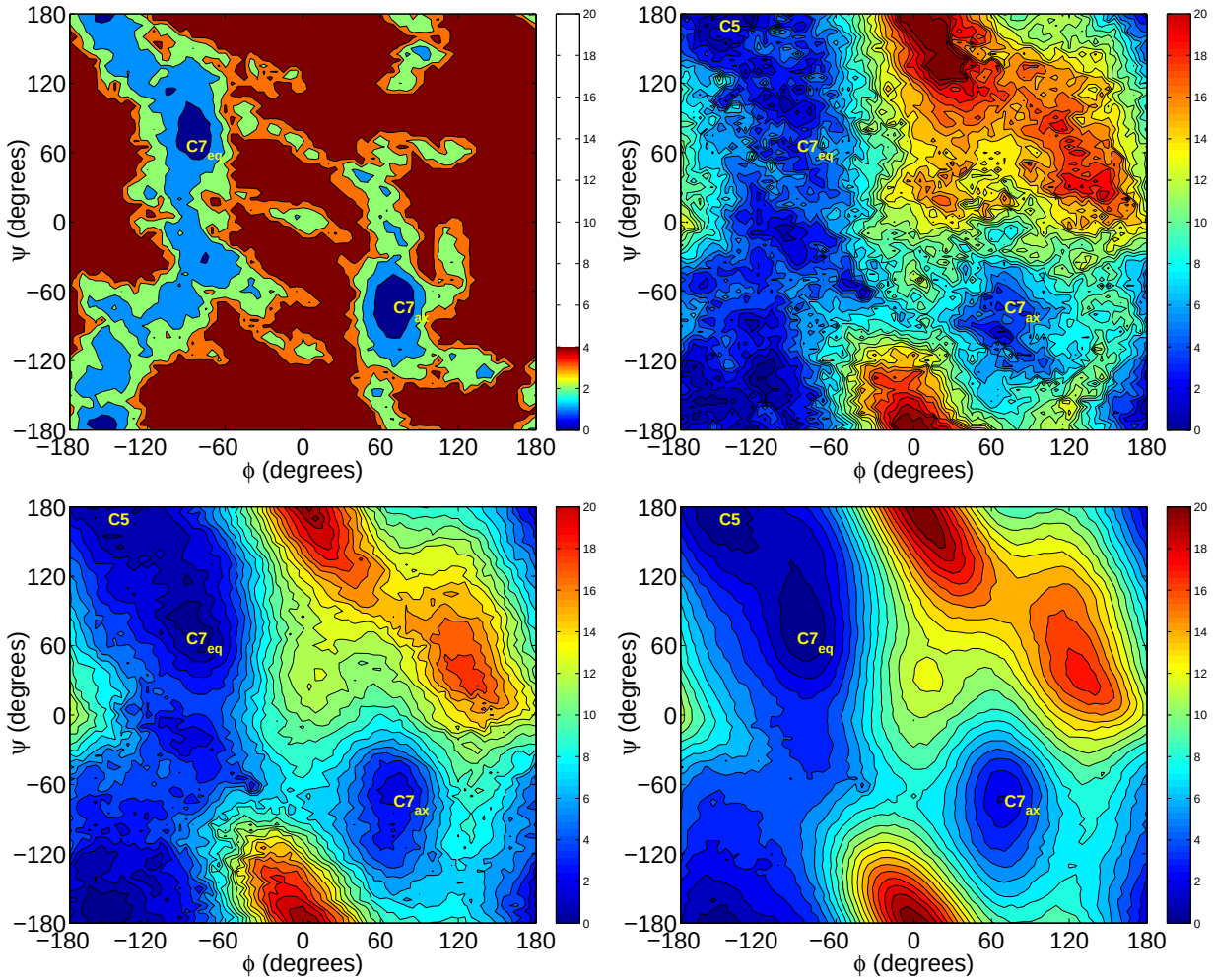

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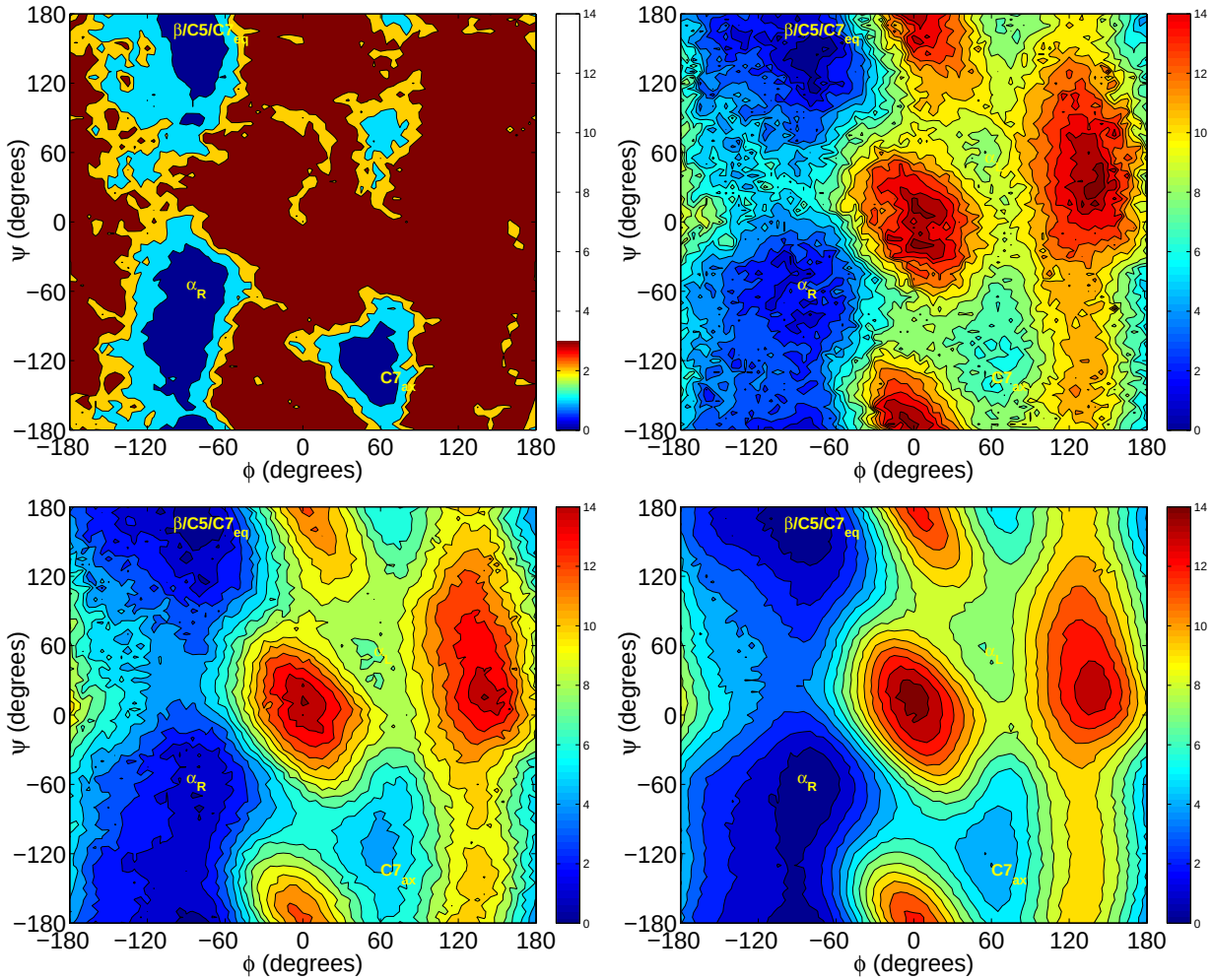

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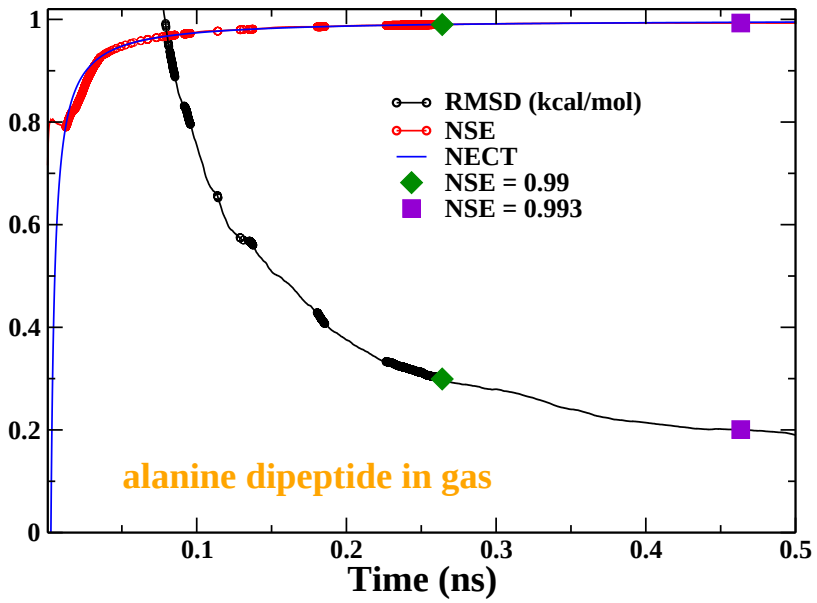

Figure 9: H.Zheng and Y. Zhang

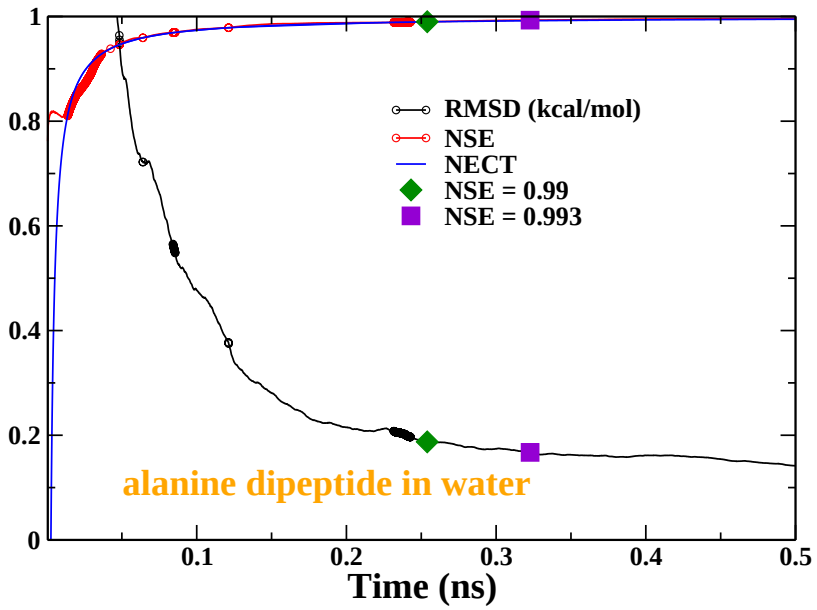

Figure 10: H.Zheng and Y. Zhang

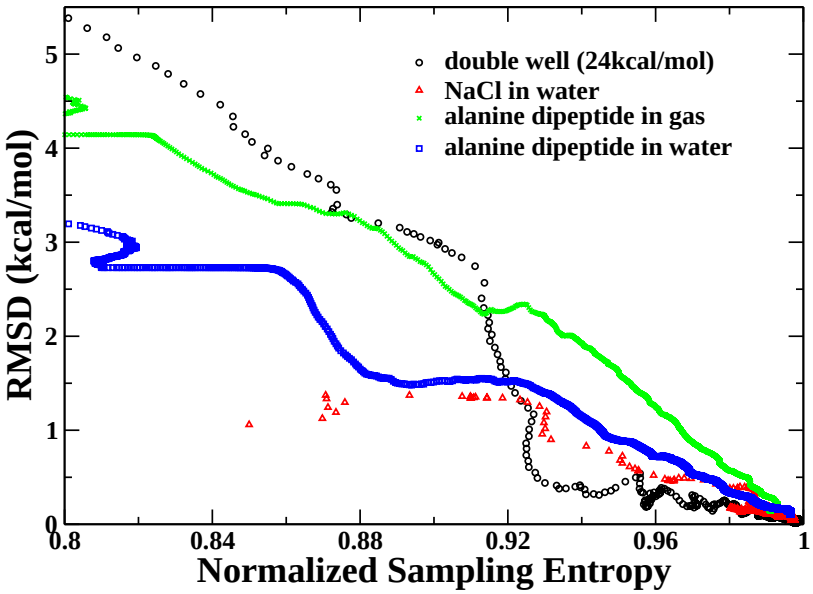

Figure 11: H.Zheng and Y. Zhang