Markov State Models with reweighting

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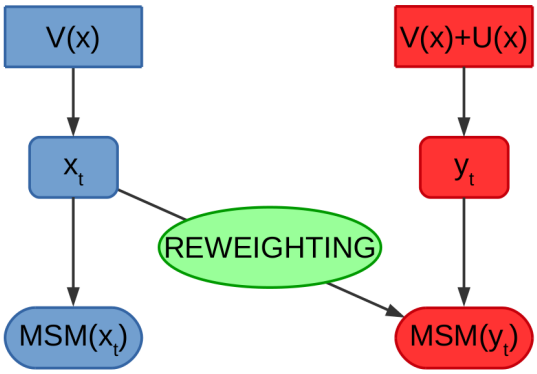

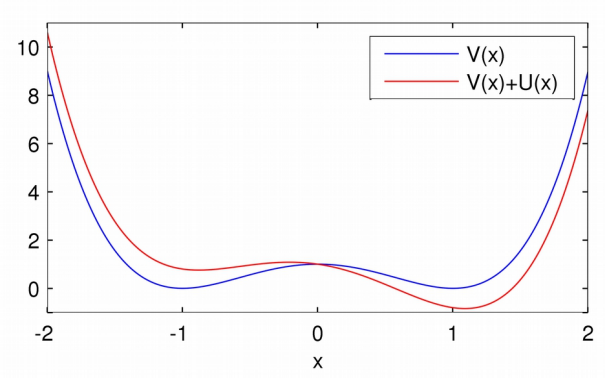

Molecular Dynamics (MD) is characterized by metastable states and transitions that occur at different timescales. Recent studies [1] have proven, through Markov State Models (MSM) analysis, that the timescales are very sensitive on the potential energy function of the molecule and that different force fields of the same molecular system show different dynamic properties. This result suggests the need to improve the current force fields analyzing the effects caused by parameters variation. To address this issue, it would be necessary to produce a MD trajectory and to construct the respective MSM, for each parameter set. This approach is computationally expensive and requires the development of a validation method that acts directly on the MSM.

Taking a force field as reference, each parameter variation can be considered as an external perturbation of the potential energy function. Because the potential energy perturbation affects the stationary distribution of the system, we can exploit the Girsanov theorem [2] to reweight the dynamics and to rewrite the transition probability matrix of the original MSM in terms of the new stationary distribution [3]. The method can be used to predict the timescales of a molecular system in a perturbed potential energy function without rerunning molecular dynamics simulation and could be relevant to force field optimization.

We performed tests of one-dimensional diffusive processes verifying the limits of applicability of the method. Then we have tested many-body systems in three-dimensional space, formulating an extension of the method when the MSM is constructed on a conformational space not directly perturbed. We present also preliminary results for alanine dipeptide and a benchmark test that shows the efficiency of the method.

[1] F. Vitalini, A. S. J. S. Mey, F. Noé and B. G. Keller, *J. Chem. Phys.*, **2015**, 142, 084101

[2] B. Øksendal, *Stochastic Differential Equations: An Introduction with Applications*, **2003**, Springer Verlag, Berlin 6th edition.

[3] Ch. Schütte, A. Nielsen and M. Weber, *Molecular Physics*, **2014**, 113, 69-78.