

Performing Metadynamics Simulations Using NAMD

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1 Introduction

In biological systems free energy calculations is used to understand the pathway of the events. It is shown that mechanisms of actions of different proteins, such as their conformational changes, binding to other proteins or ligands can be revealed and predicted by calculating the free energies. Metadynamics [1] is a widely used method for getting free energies. For a pictorial representation of the method please look at these Youtube videos:

<https://www.youtube.com/watch?v=IzEBpQ0c8TA>

<https://www.youtube.com/watch?v=SOq2xiYsGbM>

Metadynamics aims at helping the system to escape from its local minima and determines the underlying free energy surface as a function of a carefully chosen set of reaction coordinates (called Collective variables). Collective variables (CVs) are explicit functions of the system coordinates, e.g. a distance, a dihedral angle, etc. They represent the degrees of freedom of the system along which rare events are happening. Therefore, choosing the correct CVs that fully describes the slow events of the system is of crucial importance to the convergence of the calculations and the free energy values to be trusted.

In Metadynamics an additional history-dependent bias, in the form of a Gaussian is added to the systems potential:

$$V_G(S, t) = w \sum_{t'=\tau_G, 2\tau_G}^t \exp\left(-\frac{(S-s(t'))^2}{2\delta s^2}\right) \quad (1)$$

where, w is the Gaussians height, δs is the Gaussian width, τ_G is the time interval for the Gaussian deposition and $s(t) = S(x(t))$ is the value of the collective variable at time t . It is assumed in metadynamics that for a sufficiently long simulation, $V_G(S, t)$ provides an estimate of the underlying free energy [2]:

$$\lim_{t \rightarrow \infty} V_G(S, t) = -F(S) + C \quad (2)$$

Well-tempered metadynamics is a variant of metadynamics in which to facilitate the free energy barrier crossing, CVs are simulated at a higher temperature which is raised by ΔT (bias temperature) with respect to the system temperature. Unlike conventional metadynamics, the summation of bias potentials does not exactly compensate $F(S)$. In this case, the free energy of the system along a CV, S , is obtained by:

$$F(S, t) = -\frac{(T + \Delta T)}{\Delta T} V_G(S, t) \quad (3)$$

In the course of the simulation the Gaussian heights reduce according to $w = \omega \exp\left(-\frac{V_G(s, t)}{\Delta T}\right) \tau_G$, where ω is the initial bias deposition rate. Introduction of this form, prevents the risk of overfilling of the free energy regions in long simulations [3].

1.1 Goals of this tutorial

In this tutorial we enhance sample the conformational space of the ψ and ϕ dihedral angles of N-acetyl-alanine-methylamide (Ac-Ala-NHMe) which is usually referred to

as the alanine dipeptide shown in figure 1.

Specifically the reader learns:

1) How to perform metadynamics simulations using NAMD and obtain the free energy surfaces.

2) How to perform well-tempered metadynamics simulations and its difference with respect to the standard metadynamics simulations.

The file for this tutorial are deposited in the folder Homework together with the run outputs.

2 Standard metadynamics simulations

In this section, we simulate the free energy surface for a model system, alanine "dipeptide" (Ac-Ala-NHMe) in vacuum using metadynamics. As collective variables we choose its ϕ and ψ dihedral angles (see figure 1).

The metadynamics input is the following:

```
colvarsTrajFrequency      500 #How often the CV values are being written
colvarsRestartFrequency  1000

colvar {
    name dihedrall
    lowerBoundary -180.0 # The maximum and minimum values
    upperBoundary 180.0 # that CVs will get during the run

    width 15 # The width of the Gaussian hills
    dihedral { # The atom numbers forming the dihedral
        group1 { atomnumbers {5} }
        group2 { atomnumbers {7} }
        group3 { atomnumbers {9} }
        group4 { atomnumbers {15} }
    }
}

colvar {
    name dihedrall2
    lowerBoundary -180.0
    upperBoundary 180.0
    width 15
    dihedral {
        group1 { atomnumbers {7} }
        group2 { atomnumbers {9} }
        group3 { atomnumbers {15} }
        group4 { atomnumbers {17} }
    }
}

metadynamics {
```

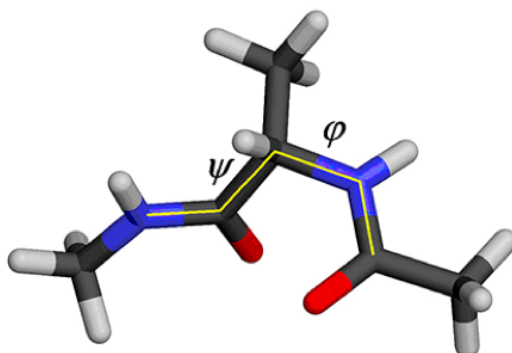


Figure 1: N-acetyl-alanine-methylamide (Ac-Ala-NHMe) called the alanine "dipeptide" structure.

```

name      meta-dihedral      # Run name
colvars   dihedrall dihedrall # List the name of the CVs
hillWeight      0.2 # The height of the Gaussian hills
newHillFrequency 500 # The frequency of hills deposition
dumpFreeEnergyFile  yes
writeHillsTrajectory  on
hillwidth      1.0
}

```

To run metadynamics simulation through NAMD, go to the Run-meta folder and run NAMD with the command:

```
namd2 +p4 meta.namd >> out
```

The relevant files for the simulation are in that folder. After running the simulation for 10 ns you are ready to plot the values of the collective variables 1 and 2 which are the ϕ and ψ angles. You will get something similar to figure 2 which shows how metadynamics helped in accelerating the sampling of these two angles.

2.1 Free energy surface

NAMD writes the free energy surface which is file ALA-meta.pmf in your working directory. We use Gnuplot to plot the surface as a function of ϕ and ψ angles. To look at the surface type the following in the terminal:

```

$gnuplot
>set pm3d
>sp "ALA-meta.pmf"

```

Now you can rotate the surface and look at different minima. We can also get a 2D plot which makes it easier for getting the free energy values. To do that, use the script

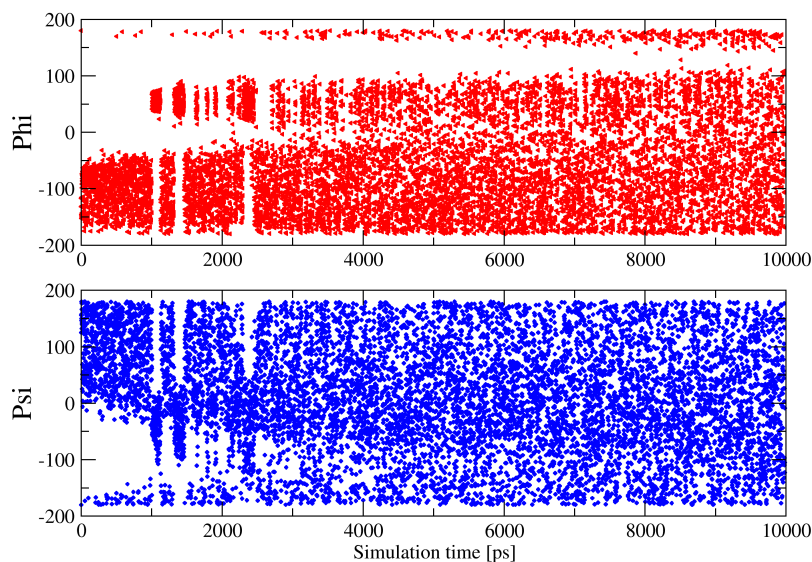


Figure 2: Starting from $(-180, 180)$ hills are deposited along the two CVs, here the two dihedral angles (ϕ and ψ) over 10 ns with metadynamics protocol.

deposited in the folder `Run-meta` to generate a contour plot. Type the following in a terminal:

```
$gnuplot
>load 'contour.pl'
```

This will generate a 2D contour plot colored by the free energy values and have a contour for every 2 kcal/mol .

3 Well-tempered metadynamics simulations

In this exercise we perform a well-tempered metadynamics on the alanine dipeptide and compare the results with normal metadynamics. One of the parameters that needs to be set is the biasing factor equals to $\frac{T+\Delta T}{T}$ and in NAMD it is determined with the `biasTemperature` which is the ΔT part.

3.1 Using a biasing factor of 6

We will perform the simulation with a `biasTemperature` of 1490 corresponding to a biasing factor of 6. Hence, in the metadynamics input we will add the following lines for well-tempered metadynamics:

```
wellTempered          on
biasTemperature       1490
```

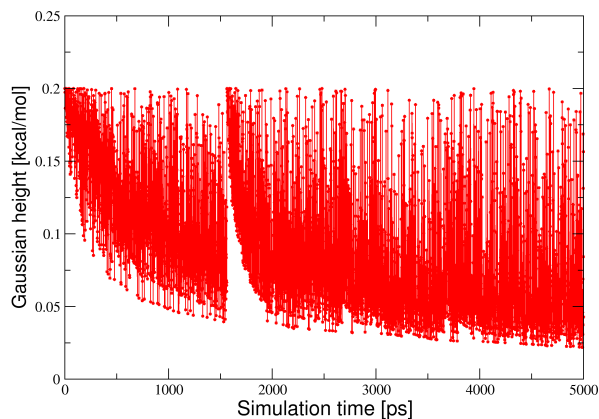


Figure 3: Gaussian hills height as a function of time rescaled according to well-tempered metadynamics.

To run a well-tempered simulation, go to the folder `Well-tempered` and launch the NAMD simulations with the input files. In figure 3 the hills height after 5 ns is shown: as you can see the hills height decreases in the course of time according to the rescaling factor of well-tempered metadynamics scheme.

References

- [1] A. Laio and M. Parrinello. Escaping free-energy minima. *Proceedings of the National Academy of Sciences*, 99(20):12562–12566, 2002.
- [2] A. Laio and F.L. Gervasio. Metadynamics: a method to simulate rare events and reconstruct the free energy in biophysics, chemistry and material science. *Reports on Progress in Physics*, 71(12):126601, 2008.
- [3] Alessandro Barducci, Giovanni Bussi, and Michele Parrinello. Well-tempered metadynamics: A smoothly converging and tunable free-energy method. *Phys. Rev. Lett.*, 100:020603, 2008.