



Improving Efficiency in SMD Simulations Through a Hybrid Differential Relaxation Algorithm “HyDRA”.

Basic Tutorial

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Introduction

Quantum mechanics (QM) has drastically changed chemists' perception and understanding of chemical reactivity. In order to explain those reactions, occurring in solution or in an enzyme at room temperature, the central object to be determined is the free energy profile (FEP) along the reaction (or the potential of mean force). For this goal, different computational implementations have been carried out. Due to the nonlinear increase of their computational cost of these implementations with system size, one strategy is to employ hybrid quantum mechanical/molecular mechanical (QM-MM) schemes. Where part of the system is treated with a quantum level (QM), while the rest of the system is described with Newtonian equations (MM).

However to determine the FEP along a given selected reaction coordinate (here called λ), either using a QM, QM-MM, or pure classical method, enhanced or biased sampling strategies are usually used. A very potent quite novel strategy for this purpose is based on performing multiple steered molecular dynamics (MSMD) simulations, which drive the system along the desired reaction coordinate under nonequilibrium conditions, using an external force. For each MSMD, the work performed by the force is determined ($W_i(\lambda)$), and they are combined using Jarzynski's Relationship (JR) 13 (eq 1) to determine the corresponding FEP ($G(\lambda)$)

equation

where $G(\lambda)$ represents the FEP as a function of the reaction coordinate, $\beta = 1/k_B T$, where k_B is Boltzmann's constant and T is the system temperature, and the brackets represent the average of the function within them.

Implementation

We have developed, validated, and applied a Hybrid QM-MM Differential Relaxation Algorithm^v HyDRA^u which allows efficient equilibration of the classical environment during a steering process that drives the QM system along a desired reaction at faster than the equilibrium (or reversible) required velocity.

IMPORTANT: Our results show the method results in accurate free energy profiles estimates, which require a smaller number of independent nonequilibrium simulations and/or can be steered faster than those using conventional QM-MM schemes.

Instalation:

Description: HyDRA is currently implemented in sander and sander Lio of the package Amber 16.09 and AmberTools 16.21

Here is the instruction to apply the patch:

HyDRA.patch is the patch for Amber16 (AmberTools 16.21, Amber 16.12 tested)

please make sure you have the correct \$AMBERHOME set and the required version updated before applying the patch

To apply the patch, just go to \$AMBERHOME and run the command

```
$ ./update_amber --apply-patch=PATH-TO-FILE/HyDRA.patch
```

you can also easily reverse the patch by

```
$ ./update_amber --reversepatch=.patches/ThirdParty16_Applied_Patches/HyDRA.patch
```

Once you have the patch applied, you need to recompile to make the changes effective

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Chorismate-Prephenate example

The conversion of chorismate to prephenate is formally a Claisen rearrangement (Figure 1). However, also is an example of an enzyme-catalyzed pericyclic process. This pathway is responsible for biosynthesis of aromatic amino acids in bacteria, fungi, and plants. We will use this process to show the capabilities of HyDRA implementation.



Figure 1. Employed reaction coordinate for the chorismate to prephenate reaction in solution and in the chorismate mutase enzyme. The distance between the two carbons, d_{cc} , is shown in blue, while d_{co} is shown in red.

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The chosen reaction coordinate was $d_{CC} - d_{CO}$ (Figure 1), which has been shown to adequately represent the process in previous works^{1,2}. In order to obtain the desired free energy profiles and thus analyze the HyDRA efficiency, we construct a chorismate molecule with 1600 surrounding water molecules (The files will be distributed with the present tutorial).

Previous works have shown that the chorismate-prephenate rearrangement is possible when the orientations of the hydroxyl group with respect to the ring adopt a Pseudo-diaxial conformation. However, NMR studies of this conformational equilibrium in solution indicated that the pseudo-diequatorial form was lower in energy than the pseudo-diaxial one. Taking this into account, we performed a molecular dynamics in order to explore the different configurations of the dihedral angle O-C-C-O, and select this snapshots to perform the SMD protocol.

Let's do it!

Production runs:

In the folder `./snapshots/` we found several restart files (`.rst7` binary files) corresponding to chorismate molecules in the pseudo-diaxial conformation. These files reached adequate density and temperature according to a standard QM-MM molecular dynamics protocol (technical details, please see paper³). The QM subsystem consists of 24 atoms corresponding to chorismate molecule. These are the coordinate files that we will use to carry out the SMD protocol.

The topology file is named as `chorismate.prmtop`, and we can find this file in the current folder. For each file, we can perform a single SMD scheme in order to obtain the work associated with the reaction process.

The definition of the reaction coordinates was saved in the `./scripts` folder and called `dist.RST`

```
#Reaction Coordinate from -3.27 to 2.00
&rst iat=8,9,5,21 rstwt=1,-1, r2=-3.27, rk2=300., r2a=2.00 /
```

Therefore, the difference with a conventional SMD protocol is that we need to add the “drar” flag in the `&qmmm` block of the `mdin` file:

`smd.mdin` example:

```
title line
&cntrl
...,
/
&qmmm
qmmask=:1'                ! Qmmm mask
...,
qm_theory='DFTB',          ! Level of Theory used
...,
drar=10,                   ! HyDRA flag.
/
DISANG=../scripts/dist.RST
DUMPAVE=dist_vs_t_1.dat    ! output file
LISTIN=POUT
LISTOUT=POUT
/
```

IMPORTANT: The criteria for the choice drar (MM steps to QM steps ratio) are discussed in the paper³ and are system dependent. For this system, we report that a drar = 10, a pulling speed of 1Å/ps and 5 curves are enough to obtain a very good estimation of the free energy profile.

Finally we run the SMD as we usually do:

```
$ cd ./output/  
$ $AMBERHOME/bin/sander -O -i ../scripts/smd.mdin -o chorismate_1_jar.mdout -p ../chorismate.prmtop  
-c ../snapshots/chorismate_1.rst7 -x chorismate_1_jar.nc -r chorismate_1_jar.rst7 -e chorismate_1_jar.mden  
-inf chorismate_1_jar.mdinfo
```

As usual, each SMD run produces a file that in the example is called dist_vs_t_1.dat. This file contains 4 columns, the value of the reaction coordinate for the nth step, the real value of the reaction coordinate, the applied force, and the work associated.

```
$ head dist_vs_t_1.dat  
-3.27000   -3.21731   -31.61363    0.00000  
-3.26789   -3.28635    11.07498    0.00876  
-3.26578   -3.19893   -40.11158    0.01480  
-3.26368   -3.24489   -11.27449    0.00297  
-3.26157   -3.28491    14.00447    0.00797  
-3.25946   -3.27622    10.05864   -0.01307  
-3.25735   -3.23669   -12.39619   -0.01695  
-3.25524   -3.29713    25.13370   -0.02573  
-3.25314   -3.25207    -0.64029   -0.01779
```

Constructing the PMF.

To build the free energy profile we need several job profiles. We can find all the necessary files in the folder ./works/with_HyDRA. Next we execute the script:

```
$ cd ./works/with_HyDRA  
$ cp ../scripts/CalcErrJarz.py .  
$ ./CalcErrJarz.py
```

If you want to re calculate de reference curve all data are available in ./works/reference

This script returns a “mse.out” file where the first column is the reaction coordinate, the second is the estimation of the free energy, and the third is the error of the estimation.

Finally, the free energy reference profile at 0.02Å/ps is found in the results/reference_FEP.dat file and the profile obtained with drar=1 and 1Å/ps in results/HyDRA_FEP.dat file.

For any suggestions/requests please send an email to eliaslopez@qb.fcen.uba.ar

References:

- 1- Martí, S., Andrés, J., Moliner, V., Silla, E., Tuñón, I., & Bertrán, J. (2003). Conformational equilibrium of chorismate. A QM/MM theoretical study combining statistical simulations and geometry optimisations in gas phase and in aqueous solution. *Journal of Molecular Structure: THEOCHEM*, 632(1-3), 197-206.
- 2- Crespo, A., Martí, M. A., Estrin, D. A., & Roitberg, A. E. (2005). Multiple-steering QM– MM calculation of the free energy profile in chorismate mutase. *Journal of the American Chemical Society*, 127(19), 6940-6941.
- 3- Ramírez, C. L., Zeida, A., Jara, G. E., Roitberg, A. E., & Martí, M. A. (2014). Improving efficiency in SMD simulations through a hybrid differential relaxation algorithm. *Journal of chemical theory and computation*, 10(10), 4609-4617.