Hamiltonian Replica Exchange MD (REST2)

- **Installation of Plumed2 merged -hrex flag, patching with Gromacs 5.1.2**

1. Download Plumed which has -hrex flag

Download **plumed2-2.3-plumedcheck2.zip** from below link.

`https://github.com/plumed/plumed2/tree/v2.3-plumedcheck2`

Step 1: Installation of PLUMED

```
unzip  plumed2-2.3-plumedcheck2.zip
cd      plumed2-2.3-plumedcheck2.zip
./configure –prefix=/path-to-install/

source  /path-to-install/sourceme.sh   ( Add this line in .bashrc)

make -j 4
make install
make doc
```

Step 3 : Patching Gromacs with PLUMED

download gromacs-5.1.2 (**http://www.gromacs.org/Downloads**)

```
tar -xvf gromacs-5.1.2.tar.gz
cd  gromacs-5.1.2/
plumed-patch -p –shared

PLUMED patching tool
1) amber14          4) gromacs-5.0.7        7) namd-2.8
2) gromacs-4.5.7    5) gromacs-5.1.2        8) namd-2.9
3) gromacs-4.6.7    6) lammps-6Apr13    9) qespresso-5.0.2
Choose the best matching code/version:
```

(Choose your gromacs-5.1.2)

Step 5 : Installation of Gromacs-5.1.2

(Ref : https://install-gromacs.blogspot.in/)

```
mkdir build
cd build/
cmake . . /
ccmake . ./
change Installation Path , MPI = ON , FFTW = fftpack
press c to configure , g to generate
cmake . . /

make -j 10
make install

add these lines in .bashrc
export PATH=$PATH:/path-to-install/bin
```

$ INSTALLATION DONE $

Verification :

Type on terminal :

```
/Path-to-install/bin/gmx_mpi mdrun -h
```

look for bellow lines

-plumed
-hrex

If you find those line , Installation successful . You are ready submit REST2 simulations.

Setting up HREMD (REST2) Simulation

(Gromacs and Plumed)

System : Alanine di peptide in water

Ref : https://arxiv.org/pdf/1307.5144.pdf
https://plumed.github.io/doc-v2.4/user-doc/html/hrex.html

Required Input Files : ala.gro , ala.top , md.mdp , plumed.dat .

Method

In Normal Replica Exchange Molecular Dynamics (REMD), each replica will be simulated at different temperatures and using different potential energy.

But, The major drawback of REMD is, The energy fluctuations are proportional to square root of No. of degrees of freedom. Which should use require large set of temperatures (replicas) for larger systems like protein in solvent.

In order to overcome this issue, HREX method has proposed and implemented in GROMACS patched with plumed. Where the potential energy of selected atoms will scaled by some parameter lambda instead using different temperatures. We know that the ensemble probability is depends on U/K_BT, a double temperature is equivalent to half the energy.

The advantage of scaling the potential energy instead of temperature is related to the fact that the energy is extensive quantity where as temperature is intensive. One can selectively choose a portion of the system to be heated.

In HREX method, They have split the system in two regions, H (hot) and C (cold), so that each atom is statistically assigned to either H or C region.

So, In classical simulations we get potential energy from defined force fields parameters. In order to scale potential energy, the force field parameters which contribute to the PE and energy barrier are charges, proper dihedral, electrostatics , Lennard-jones are scaled by some factor (lambda).

Read this jouranl to get more details on how these force fields are scaled.
https://arxiv.org/pdf/1307.5144.pdf

Prepare Inputs :

Step 1 : I would like to do 5 replicas in the temp range 300 to 1000 K .
consider 5 gro files .
ala_0.gro ala_1.gro ala_2.gro ala_3.gro ala_4.gro

Step 2 : We need to scale the force fields parameters in order to do HREMD. Or Solute Tempering (REST2). We can do this by using plumed partial-tempering command as above.

Generate the scaled topologies with plumed partial-tempering command.

```
plumed partial_tempering lamda < ala.top > scaled.top
```

Plumed partial-tempering scales the topologies of [atomtypes] section where each "hot" atom has a "_" (underscore) appended to atom type and [atoms].
Example : Change your topologies as like this

- **Plumed partial-tempering will make following changes in topology.**

```
[ atomtypes ]
; name at.num  mass  charge ptype  sigma    epsilon
HC  1  1.00800 0.000000 A 0.264953 0.0656888
HC_ HC 1.00800 0.000000 A 0.264953 0.0359792  ; scaled
CT  6 12.01000 0.000000 A 0.339967 0.45773
```

```
CT_ CT 12.01000 0.000000 A 0.339967 0.250709  ; scaled
```

- You should manually select hot atoms which you want by appended underscore to the atom types (“HC_”).

```
[ atoms ]
;      nr    type  resnr  residue    atom  cgnr    charge
mass  typeB    chargeB      massB
; residue    1 ACE rtp ACE q 0.0
1 HC_ 1 ACE HH31 1 0.0831113 1.0080 ; qtot 0.1123
2 CT_ 1 ACE CH3 2 -0.271018 12.0100 ; qtot -0.2539
3 HC_ 1 ACE HH32 3 0.0831113 1.0080 ; qtot -0.1416
```

```
ala_scaled_0.top    ala_scaled_1.top    ala_scaled_2.top
ala_scaled_3.top    ala_scaled_4.top
```

Step 3: We require gromacs input file (file.mdp) with required parameters nsteps, temperature etc. (Note We no need to use different temperature here , beacause we are not dealing with temperatures instead we are modifying potential) and plumed input file (plumed.dat) ,without plumed.dat file -hrex will not run.

```
File.mdp    plumed.dat
```

Step 4 : Create a gromacs binary input files (file.tpr) to run gromacs simulation by using above scaled topologies and nvt.mdp and all gro files.

```
gmx_mpi grompp -f file.mdp -p ala_scaled_$i.top -o hremd_$i.tpr -maxwarn 1
```

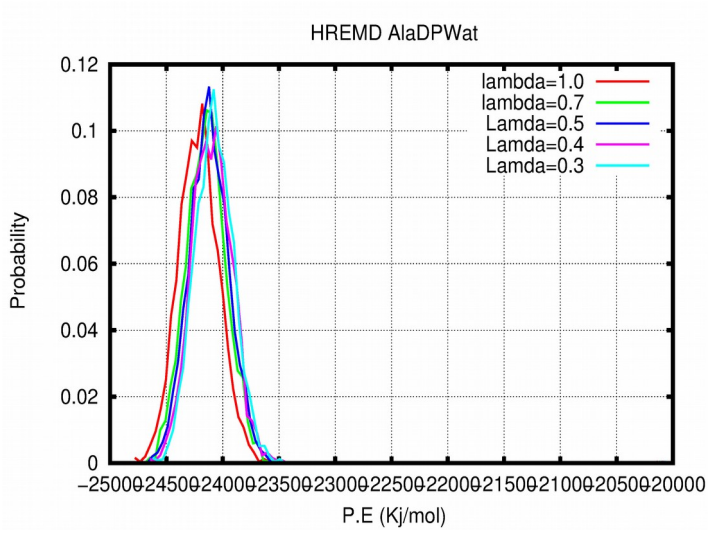
Now , hremd_0.tpr hremd_1.tpr hremd_2.tpr hremd_3.tpr hremd_4.tpr files will generate.
Step 5 : Submit simulation by using this gromacs command.

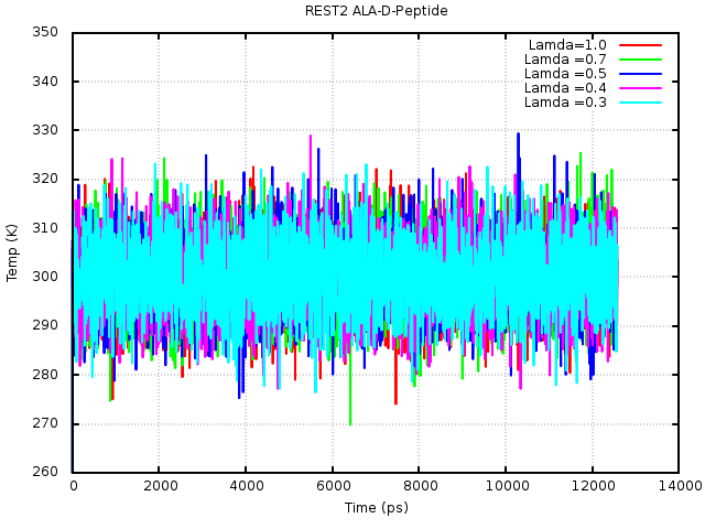
```
mpirun -np 5 gmx_mpi mdrun -v -deffnm hremd_ -plumed plumed.dat -multi 5 -replex 1000 -hrex
```

Bash Script to produce inputs for hremd. (REST2)

```
#five replicas
nrep=5
# "effective" temperature range
tmin=300
tmax=1000
# build geometric progression
list=$(
awk -v n=$nrep \
    -v tmin=$tmin \
    -v tmax=$tmax \
  'BEGIN{for(i=0;i<n;i++){
    t=tmin*exp(i*log(tmax/tmin)/(n-1));
    printf(t); if(i<n-1)printf(",");
  }
}'
)
# clean directory
rm -fr \#*
rm -fr topol*
for((i=0;i<nrep;i++))
do
# choose lambda as T[0]/T[i]
# remember that high temperature is equivalent to low lambda
  lambda=$(echo $list | awk 'BEGIN{FS=",";}{print $1/$'$((i+1))';}')
# process topology, # (if you are curious, try "diff topol0.top topol1.top" to see the changes)
  plumed partial_tempering  $lambda < ala.top > ala_scaled_$i.top
# prepare tpr file, -maxwarn is often needed because box could be charged
   gmx_mpi  grompp  -f  file.mdp  -p  ala_scaled_$i.top  -o  hremd_$i.tpr -maxwarn 1
done
#=================================================#
  mpirun  -np  5  gmx_mpi   mdrun  -v  -deffnm  hremd_  -plumed  plumed.dat -multi  5 -replex 100  -hrex
```

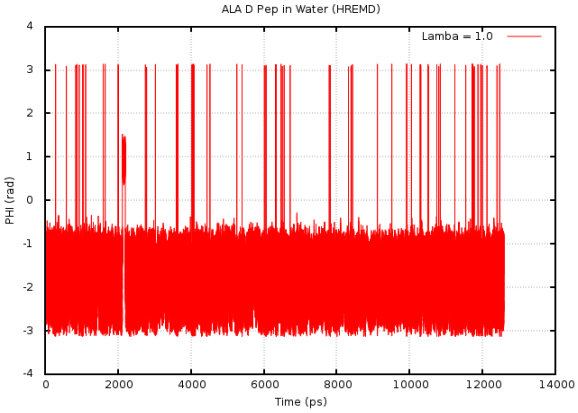
ANALYSIS

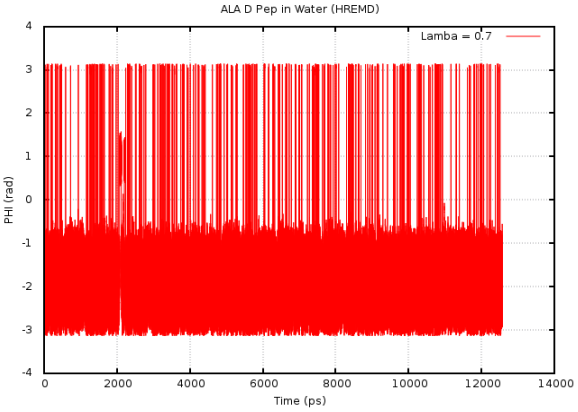


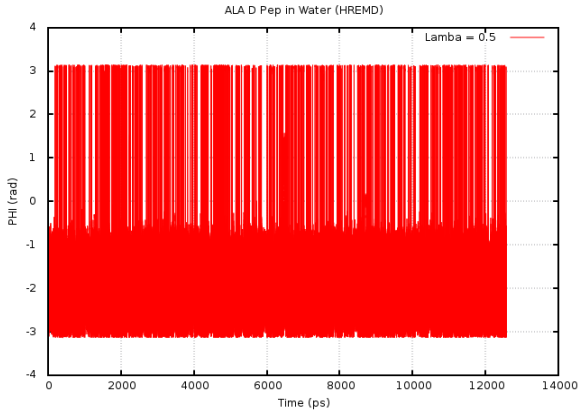


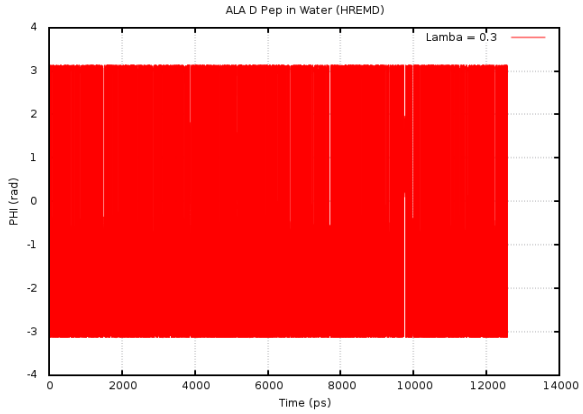
- Temp is not changing with Lamda but , Enhansing sampling in configuration space by scaling potential.

Time vs PHI

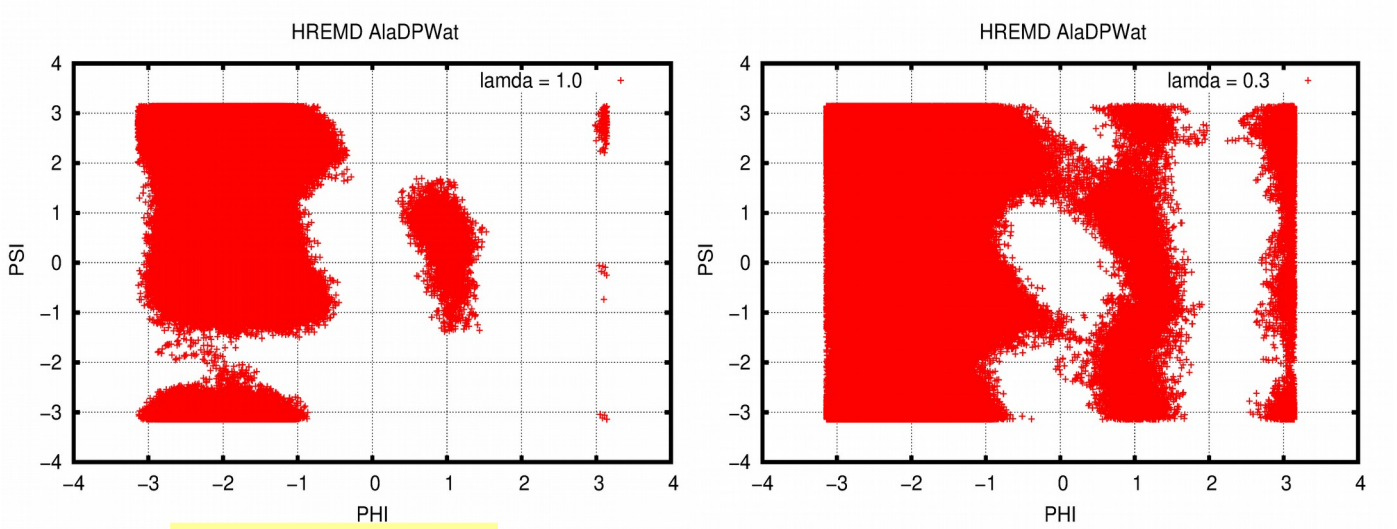








PHI vs PSI



Lamda = 1.0

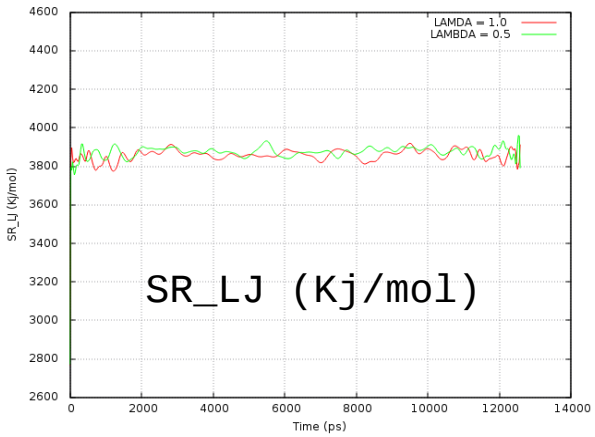
Lamda = 0.3

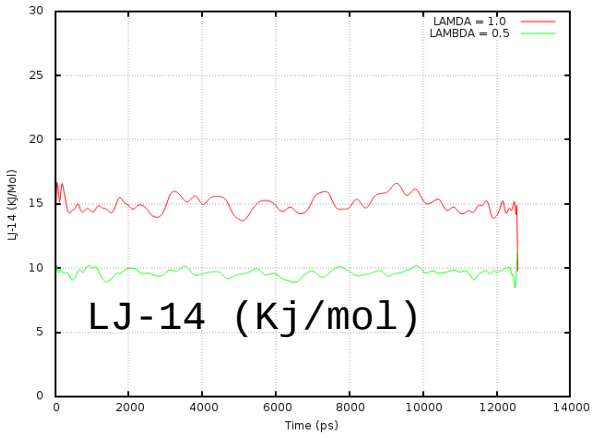
- It can be seen that conformational space explored by the replica at lamda=0.3 is larger than replica at lamda 1.0

Comparing lambda = 1.0 to lambda = 0.5

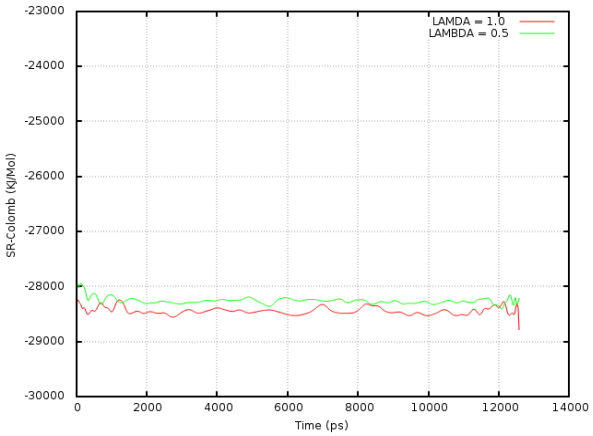
Verification :

All the energies for lambda = 0.5 is half of that lambda = 1.0

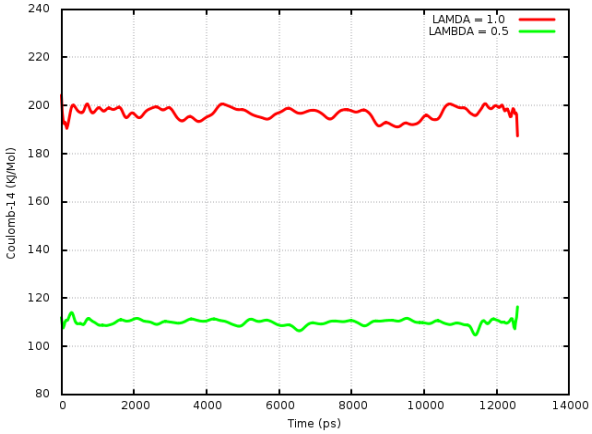




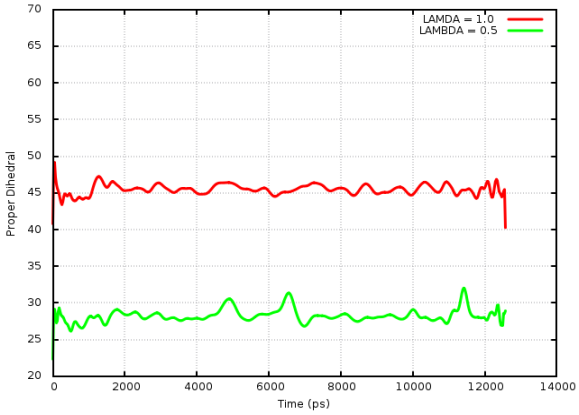
SR_columb (Kj/mol)



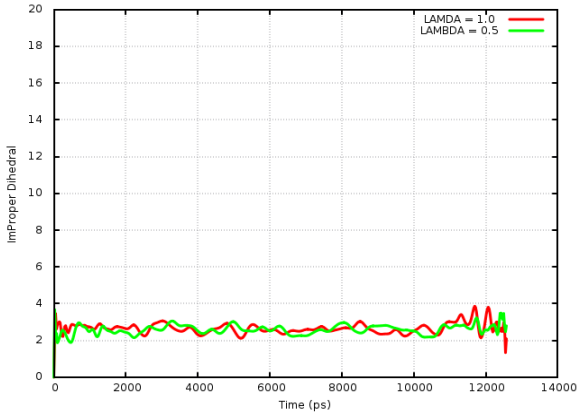
Culumb_14 (Kj/mol)



Proper Dihedral (rad)

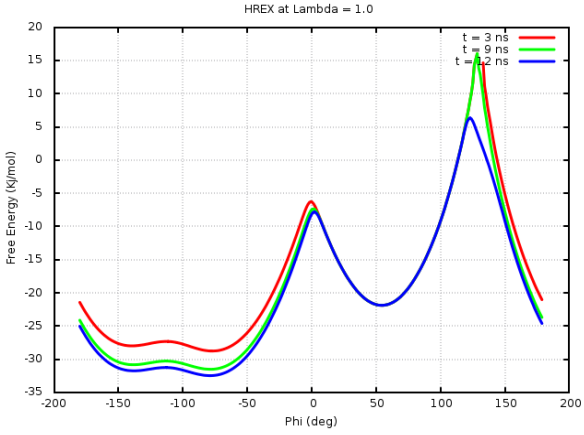


Improper Dihedral(rad)



Free Energy : and CONVERGENCE are got using plumed sumhill program.

Free Energy Profile



Convergence of FES