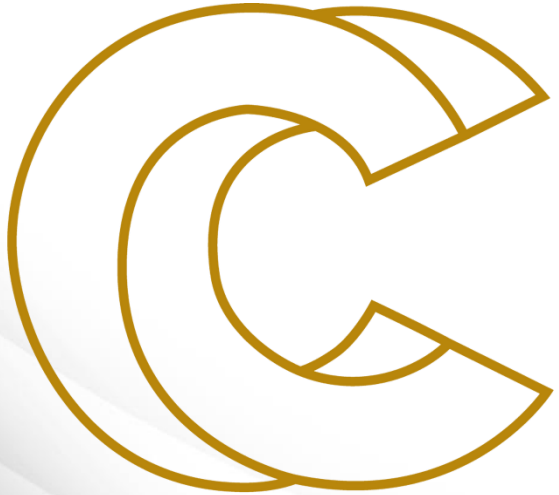

EURO 4SEE

MM/GB(P)SA free energy calculations using various programs

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Lesson 3: MM/PBSA calculation using gmx_MMPSA

General Information about gmx_MMPBSA

- gmx_MMPSA is a tool based on AMBER's MMPBSA.py aiming to perform end-state free energy calculations with GROMACS files.
- It is compatible with all GROMACS versions and requires AmberTools (version 20 or higher).
- Uses sander to calculate energy values
- Has analysis tools: ex: interactive visualization of per-residue energy contributions on the PDB structure using PyMOL, interactive charts

Workflow for gmx_MMPBSA

Topology Preparation

- Convert GROMACS topology with parmed into amber topology
- Creating complex, receptor and ligand protein structure files

Trajectory Preparation

- Post Processing the trajectory file (Removing water molecules etc.)
- Convert GROMACS trajectory with cpptraj into amber trajectory

Calculations

- Calculating the gas-phase energy with sander
- Calculating the PB or GB
- Calculate the SASA term

Visualization Analysis

- Analysis of the results and exporting to text, pdb files etc.

What programs do you need?

Requirements

- GROMACS (series 4.x.x or 5.x.x or 20xx.x)
- AmberTools ≥ 20
- python ≥ 3.11
- mpi4py=4.0.1 for multicore computations

How to install gmx_MMPSA on HPC

https://valdes-tresanco-ms.github.io/gmx_MMPBSA/dev/installation/

- Download environment yml file (env.yml) that contains dependency information
- Load anaconda

$ module load ANACONDA/Anaconda3-2024.06-1-python-3.12

$ source /ari/progs/ANACONDA/Anaconda3-2024.06-1-python-3.12/etc/profile.d/conda.sh

- Create a new environment and use the *.yml file to install dependencies

$ conda env create --file env.yml

- To use gmx_MMPBSA, just activate the environment

$ conda activate gmxMMPBSA

How to install gmx_MMPSA on HPC

https://valdes-tresanco-ms.github.io/gmx_MMPBSA/dev/installation/

- Alternatively use pip
- Create a new environment and activate it

$ conda create -n gmxMMPBSA python=3.11.8 -y –q

$ conda activate gmxMMPBSA

Install mpi4py and AmberTools

$conda install -c conda-forge "mpi4py=4.0.1" "ambertools<=23.3" -y -q

Install dependencies for ploting

$ conda install -c conda-forge "numpy=1.26.4" "matplotlib=3.7.3" "scipy=1.14.1" "pandas=1.5.3" "seaborn=0.11.2" -y -q

(Optional) Install GROMACS

$ conda install -c conda-forge "gromacs<=2023.4" pocl -y –q

$ python -m pip install gmx_MMPBSA

gmx_MMPSA input file

mmpbsa.in

```
&general
  startframe           = 1          # First frame to analyze
  endframe             = 10         # Last frame to analyze
  interval             = 1          # Number of frames between adjacent frames analyzed
  PBRadii              = 5          # Define PBRadii to build amber topology from GROMACS files
  temperature          = 298.15     # Temperature
  full_traj            = 0          # Print a full traj. AND the thread trajectories
  keep_files           = 2          # How many files to keep after successful completion
  verbose              = 1          # How many energy terms to print in the final output
/
&pb
  ipb                  = 2          # Dielectric model for PB
  inp                  = 1          # Nonpolar solvation method
  indi                 = 1.0        # Internal dielectric constant
  exdi                 = 80.0       # External dielectric constant
  smoothopt            = 1          # Set up dielectric values for finite-difference grid edges
  istrng               = 0.150      # Ionic strength (M)
  prbrad               = 1.4        # Probe radius
  iprob                = 2.0        # Mobile ion probe radius (Angstroms) for ion accessible surface used to define the Stern layer
  sasopt               = 0          # Use the solvent excluded surface
  nbuffer              = 0.0        # Sets how far away (in grid units) the boundary of the finite difference grid is away from the solute surface
  nfocus               = 2          # Electrostatic focusing calculation
  fscale               = 8          # Set the ratio between the coarse and fine grid spacings in an electrostatic focussing calculation
  bcopt                = 5          # Boundary condition option
  eneopt               = 2          # Compute electrostatic energy and forces
  cutnb                = 0.0        # Cutoff for nonbonded interations
  use_rmin             = 1          # The option to set up van der Waals radii
  sprob                = 0.557      # Solvent probe radius for SASA used to compute the dispersion term
  vprob                = 1.3        # Solvent probe radius for molecular volume (the volume enclosed by SASA)
  use_sav              = 1          # Use molecular volume (the volume enclosed by SASA) for cavity term calculation
  cavity_surften       = 0.0378     # Surface tension
  cavity_offset        = -0.5692    # Offset for nonpolar solvation calc
  maxsph               = 400        # Approximate number of dots to represent the maximum atomic solvent accessible surface
/
```

Slurm file

- Load necessary modules
- Here is the parallelized version of MMPBSA computation

```
#SBATCH --output=slurm-%j.out
#SBATCH --error=slurm-%j.err

module load ANACONDA/Anaconda3-2024.06-1-python-3.12
source /ari/progs/ANACONDA/Anaconda3-2024.06-1-python-3.12/etc/profile.d/conda.sh

mpirun -np 5 gmx_MMPBSA -O -i mmpbsa.in -cs com.tpr -ct com_traj.xtc -ci index.ndx -cg 3 4 -cp topol.top
-nogui -o FINAL_RESULTS_MMPBSA.dat -eo FINAL_RESULTS_MMPBSA.csv
```

Output log file

```
|
|gmx_MMPBSA Version=1.6.4 based on MMPBSA.py v.16.0
|Complex Structure file:                                        com.tpr
|Complex (GROMACS) topology file:                            topol.top
|Complex (AMBER) topology file:                             COM.prmtop
|Receptor (AMBER) topology file:                            REC.prmtop
|Ligand (AMBER) topology file:                              LIG.prmtop
|Initial trajectories:                                   COM_traj_0.xtc
|
|Receptor mask:                 ":1-58"
|Ligand mask:                   ":59"
|Ligand residue name is:        "36X"
|
|Calculations performed using 10 complex frames
|Poisson Boltzmann calculations performed using internal PBSA solver in sander
|
|Using temperature = 298.15 K
|All units are reported in kcal/mol
|
|SD - Sample standard deviation, SEM - Sample standard error of the mean
|SD(Prop.), SEM(Prop.) - SD and SEM obtained with propagation of uncertainty formula
|https://en.wikipedia.org/wiki/Propagation_of_uncertainty#Example_formulae
|
-------------------------------------------------------------------------------
```

```
-------------------------------------------------------------------------------

POISSON BOLTZMANN:

Complex:
Energy Component       Average     SD(Prop.)          SD   SEM(Prop.)         SEM
-------------------------------------------------------------------------------
BOND                    177.84         10.13       10.13         3.20        3.20
ANGLE                   445.26         10.53       10.53         3.33        3.33
DIHED                   732.12          7.30        7.30         2.31        2.31
VDWAALS                -422.56          7.44        7.44         2.35        2.35
EEL                   -3760.08         22.56       22.56         7.13        7.13
1-4 VDW                 211.08          3.91        3.91         1.24        1.24
1-4 EEL                2584.18         17.90       17.90         5.66        5.66
EPB                   -1294.09         13.57       13.57         4.29        4.29
ENPOLAR                  20.70          0.13        0.13         0.04        0.04
EDISPER                   0.00          0.00        0.00         0.00        0.00

GGAS                    -32.16         34.16       13.81        10.80        4.37
GSOLV                 -1273.39         13.57       13.56         4.29        4.29

TOTAL                 -1305.55         36.75        9.72        11.62        3.07

-------------------------------------------------------------------------------
```

```
-------------------------------------------------------------------------------
Receptor:
Energy Component       Average     SD(Prop.)          SD   SEM(Prop.)         SEM
-------------------------------------------------------------------------------
BOND                    172.67          9.99        9.99         3.16        3.16
ANGLE                   403.04         10.86       10.86         3.44        3.44
DIHED                   719.09          6.47        6.47         2.05        2.05
VDWAALS                -396.81          6.07        6.07         1.92        1.92
EEL                   -3772.98         21.36       21.36         6.75        6.75
1-4 VDW                 206.74          3.99        3.99         1.26        1.26
1-4 EEL                2657.80         17.84       17.84         5.64        5.64
EPB                   -1298.64         13.51       13.51         4.27        4.27
ENPOLAR                  20.69          0.14        0.14         0.04        0.04
EDISPER                   0.00          0.00        0.00         0.00        0.00

GGAS                    -10.44         32.97       14.27        10.43        4.51
GSOLV                 -1277.95         13.51       13.52         4.27        4.28

TOTAL                 -1288.39         35.63        9.85        11.27        3.12

-------------------------------------------------------------------------------
```

```
-------------------------------------------------------------------------------
Ligand:
Energy Component       Average     SD(Prop.)          SD   SEM(Prop.)         SEM
-------------------------------------------------------------------------------
BOND                      5.17          1.28        1.28         0.40        0.40
ANGLE                    42.22          4.24        4.24         1.34        1.34
DIHED                    13.02          2.50        2.50         0.79        0.79
VDWAALS                  -2.18          0.19        0.19         0.06        0.06
EEL                      20.01          0.43        0.43         0.13        0.13
1-4 VDW                   4.34          0.65        0.65         0.21        0.21
1-4 EEL                 -73.62          0.82        0.82         0.26        0.26
EPB                     -12.73          0.25        0.25         0.08        0.08
ENPOLAR                   2.05          0.01        0.01         0.00        0.00
EDISPER                   0.00          0.00        0.00         0.00        0.00

GGAS                      8.97          5.21        2.66         1.65        0.84
GSOLV                   -10.68          0.25        0.25         0.08        0.08

TOTAL                    -1.71          5.22        2.76         1.65        0.87

-------------------------------------------------------------------------------
```

```
-------------------------------------------------------------------------------
Delta (Complex - Receptor - Ligand):
Energy Component       Average     SD(Prop.)          SD   SEM(Prop.)         SEM
-------------------------------------------------------------------------------
ΔBOND                     0.00          1.14        0.00         0.36        0.00
ΔANGLE                   -0.00          3.90        0.00         1.23        0.00
ΔDIHED                   -0.00          1.67        0.00         0.53        0.00
ΔVDWAALS                -23.57          1.18        2.83         0.37        0.90
ΔEEL                     -7.11          0.77        3.19         0.24        1.01
Δ1-4 VDW                 -0.00          0.57        0.00         0.18        0.00
Δ1-4 EEL                  0.00          0.77        0.00         0.24        0.00
ΔEPB                     17.28          0.19        2.86         0.06        0.91
ΔENPOLAR                 -2.05          0.00        0.08         0.00        0.02
ΔEDISPER                  0.00          0.00        0.00         0.00        0.00

ΔGGAS                   -30.68          1.41        4.05         0.45        1.28
ΔGSOLV                   15.23          0.19        2.82         0.06        0.89

ΔTOTAL                  -15.45          1.43        2.17         0.45        0.69
-------------------------------------------------------------------------------
-------------------------------------------------------------------------------
```

References

https://valdes-tresanco-ms.github.io/gmx_MMPBSA/dev/
https://github.com/Valdes-Tresanco-MS/gmx_MMPBSA/tree/master

Valdés-Tresanco, M.S., Valdés-Tresanco, M.E., Valiente, P.A. and Moreno E. **gmx_MMPBSA: A New Tool to Perform End-State Free Energy Calculations with GROMACS**. *Journal of Chemical Theory and Computation*, 2021 17 (10), 6281-6291 https://pubs.acs.org/doi/10.1021/acs.jctc.1c00645

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