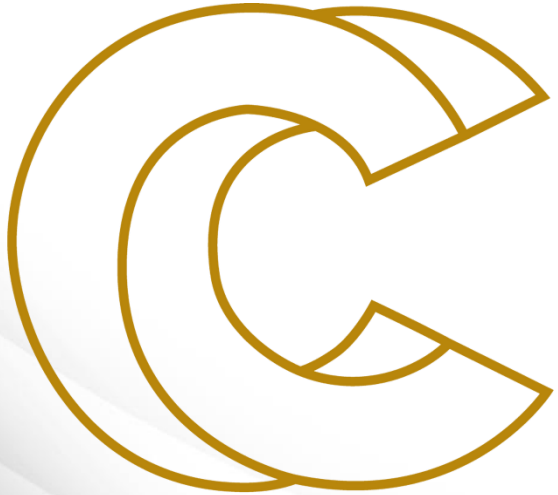

EURO 4SEE

MM/G(P)BSA free energy calculations using various programs

Assoc.Prof Sefer BADAY
Istanbul Technical University, Informatics Institute
ncc@ulakbim.gov.tr

Lesson 2: MM/GB(P)SA Using AmberTools

General Information

- Can run both MM/GBSA and MM/PBSA calculations
- Allows single trajectory and multiple trajectory calculations
- Allows different Entropy calculation methods (quasi-harmonic approximation or the normal mode approximation)
- Alanine scanning with either PB or GB implicit solvent models
- MM/PBSA calculation for ligand binding to a membrane protein

Installing Ambertools using Anaconda

- Firstly, Anaconda module should be loaded before installing AmberTools23
- You can run the following commands on the terminal on UHEM
- $ module load ANACONDA/Anaconda3-2023.03-python-3.9
- $ source /ari/progs/ANACONDA/Anaconda3-2023.03-python-3.9/etc/profile.d/conda.sh
- Then, a new conda environment is created:
- $ conda create --name AmberTools23
- $ conda activate AmberTools23
- To install the amber tools under the AmberTools23 environment type this command:
- $ conda install -c conda-forge ambertools=23

Installing Ambertools using Anaconda

- **To run MMPBSA.py parallel**, mpi4py module should be installed (You might be load MPI/mpich-4.1-gcc-9.4.0 module before installing mpi4py) :
- $ conda install -c conda-forge mpi4py mpich
- Installing CPPTRAJ under the AmberTools23 environment
- First, you need to change directory to the
- $ cd /ari/users/<user_name>/.conda/envs/AmberTools23/Ambertools/src/cpptraj
- Cpptraj files are obtained via git clone:
- $ git clone https://github.com/Amber-MD/cpptraj.git

Processing trajectory file

Stripping solvated complex into a dry complex, receptor and ligand

- Since the MM/PB(GB)SA calculations are based on an implicit solvent model, we need to obtain the dry complex, receptor, and ligand topology files.
- The dry complex topology file is created from the solvated topology file by stripping water molecules and ions using the -s option.
- It is suggested to mask either the residue number or atom index of the receptor so that the complex topology file can be split into receptor and ligand.
- (For details on atom selection, check the cpptraj user guide).
- For this purpose, the ante-MMPBSA.py script is used:
-
- $ ante-MMPBSA.py -p step3_input.prmtop -c complex.prmtop -r receptor.prmtop -l ligand.prmtop -m <receptor residue range> -s :TIP3:POT(or SOD):CLA --radii bondi
- By running this command, complex, receptor and ligand topology files are created one after another.

Preparing configuration file for MMPBSA.py

- This configuration file is created for MMGBSA calculation.
- You can check Amber 2024 Reference Manual for details about the parameters in the configuration file.
- Create text file named mmgbsa.in

```
&general
 startframe=1, endframe=10000, verbose=1,keep_files=0, strip_mask=':TIP3:POT:CLA',
/
&gb
 igb=7, saltcon=0.150,
/
```

General refers to general paramaters
Gb refers to parameters related to Generalized Born calculations
Igb parameter is specific protocol for how GB is calculated. Check the manual

Running MM/GBSA.py.MPI in UHEM

- **Parallel execution is a huge plus**
- **Put the following code in the job file**
- module load ANACONDA/Anaconda3-2023.03-python-3.9
- source /ari/progs/ANACONDA/Anaconda3-2023.03-python-3.9/etc/profile.d/conda.sh
- conda activate AmberTools23
- mpirun -np **124** MMPBSA.py.MPI -O -i /path-to-config/mmpbsa.in -o /path-to-output/FINAL_RESULTS_MMPBSA.dat -sp /path-to-solvated-complex/step3_input.prmtop -cp /path-to-dry-complex/complex.prmtop -rp /path-to-receptor/receptor.prmtop -lp /path-to-ligand/ligand.prmtop -y /path-to-trajectory/all_frames.nc > progress.log
- wait

Log file

```
Loading and checking parameter files for compatibility...
CHAMBER prmtops found. Forcing use of sander
cpptraj found! Using /ari/users/sbaday/.conda/envs/AmberTools23/bin/cpptraj
sander found! Using /ari/users/sbaday/.conda/envs/AmberTools23/bin/sander
Preparing trajectories for simulation...
5000 frames were processed by cpptraj for use in calculation.

Running calculations on normal system...

Beginning GB calculations with /ari/users/sbaday/.conda/envs/AmberTools23/bin/sande
  calculating complex contribution...
  calculating receptor contribution...
  calculating ligand contribution...

Timing:
Total setup time:                          0.267 min.
Creating trajectories with cpptraj:        0.814 min.
Total calculation time:                    2.898 min.

Total GB calculation time:                 2.853 min.

Statistics calculation & output writing:   0.002 min.
Total time taken:                          3.996 min.


MMPBSA.py Finished! Thank you for using. Please cite us if you publish this work
with this paper:
   Miller III, B. R., McGee Jr., T. D., Swails, J. M. Homeyer, N. Gohlke, H. and
Roitberg, A. E.
   J. Chem. Theory Comput., 2012, 8 (9) pp 3314--3321
```

Output file

|
|Generalized Born ESURF calculated using 'LCPO' surface areas
|
|All units are reported in kcal/mole.

GENERALIZED BORN:

Complex:

Energy Component	Average	Std. Dev.	Std. Err. of Mean
VDWAALS	-1312.8884	19.1530	0.2709
EEL	-11027.2883	87.8149	1.2419
EGB	-2926.5235	71.2143	1.0071
ESURF	73.7185	1.6116	0.0228
G gas	-12340.1767	87.4339	1.2365
G solv	-2852.8050	70.7223	1.0002
TOTAL	-15192.9817	40.3329	0.5704

Receptor:

Energy Component	Average	Std. Dev.	Std. Err. of Mean
VDWAALS	-1178.2226	17.3667	0.2456
EEL	-10849.1395	84.3668	1.1931
EGB	-2629.2005	67.8392	0.9594
ESURF	70.6157	1.4179	0.0201
G gas	-12027.3621	83.4714	1.1805
G solv	-2558.5848	67.3512	0.9525
TOTAL	-14585.9468	38.1584	0.5396

Ligand:

Energy Component	Average	Std. Dev.	Std. Err. of Mean
VDWAALS	-71.5269	4.1901	0.0593
EEL	-123.9350	18.3081	0.2589
EGB	-381.1140	12.2852	0.1737
ESURF	12.1227	0.4498	0.0064
G gas	-195.4619	17.2761	0.2443
G solv	-368.9912	12.4968	0.1767
TOTAL	-564.4531	11.3363	0.1603

Differences (Complex - Receptor - Ligand):

Energy Component	Average	Std. Dev.	Std. Err. of Mean
VDWAALS	-63.1390	7.8121	0.1105
EEL	-54.2138	41.3443	0.5847
EGB	83.7909	37.7880	0.5344
ESURF	-9.0200	0.9597	0.0136
DELTA G gas	-117.3528	40.7184	0.5758
DELTA G solv	74.7710	37.6250	0.5321
DELTA TOTAL	-42.5818	8.1617	0.1154

Converting NAMD files

- We can convert CHARMM topology files (psf) and NAMD trajectory files (dcd) so that we can use Ambertools to perform MM/GBSA or MM/PBSA

- To convert charmm *.psf and *.crd files to amber topology files, the chamber module under parmed should be used. Here is the basic command to load charmm files:
- parmed
- chamber -top /path-to-toppar/toppar/*.rtf -param /path-to-toppar /toppar/*.prm -str /path-to-toppar /toppar/*.str -psf step3_input.psf -crd step3_input.crd -radii bondi
- A radii option should be set for calculation using implicit solvent model.
- The radius bondi is selected for atoms created by Charmm force-field.
- There are also amber6, mbondi, mbondi2, and mbondi3 radius set.

Converting NAMD files

- After the given parameter and topology files are read by the module, we are ready to write amber topology files:
- Outparm step3_input.prmtop step3_input.inpcrd
- go

```
[sbaday@altay:~ ]$ module load ANACONDA/Anaconda3-2023.03-python-3.9
Anaconda icin bu module ilaveten asagidaki komutu da calistiriniz:
source /ari/progs/ANACONDA/Anaconda3-2023.03-python-3.9/etc/profile.d/conda.sh

[sbaday@altay:~ ]$ source /ari/progs/ANACONDA/Anaconda3-2023.03-python-3.9/etc/profile.d/conda.sh

[sbaday@altay:~ ]$ conda activate AmberTools23
(AmberTools23) parmed

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ParmEd: a Parameter file Editor


Reading input from STDIN...
> chamber
```

Converting NAMD files

Converting *.dcd file to *.mdcrd file (or *.nc file)

- The MMPBSA.py script cannot read charmm trajectory files.
- Therefore, the DCD file is converted to amber trajectory file (*.mdcrd or *.nc) using cpptraj program:
- $ cpptraj
- parm /path-to-the/step3_input.psf
- trajin /path-to-the/ .dcd
- trajout all_frames.mdcrd mdcrd (or trajout all_frames.nc nc)
- Run
- or you can type all these commands into a script and run $ cpptraj <script_name>.cpptraj

References

- ***MMPBSA.py reference:*** Miller III, B. R., McGee Jr., T. D., Swails, J. M. Homeyer, N. Gohlke, H. and Roitberg, A. E. J. Chem. Theory Comput., 2012, 8 (9) pp 3314--3321
  You can get the ambertools download file and manual from the following link: https://ambermd.org/AmberTools.php

Next lecture

- We will see how we can run MM/GB(P)SA calculations using gmx_MMPBSA

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Thanks!

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