MM/GBSA tutorials for SARS-CoV-2 Mpro in complex with inhibitor N3 by MolAICal and NAMD

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1. Introduction

In this tutorial, the MolAICal (https://doi.org/10.1093/bib/bbaa161) is used to calculate the MM/GBSA between ligand N3 and SARS-CoV-2 Mpro based on molecular dynamical (MD) simulated results by NAMD. This tutorial is just a demo. To save running and storage space, only 25 frames of MD simulated trajectories of SARS-CoV-2 Mpro in complex with N3 are selected for this tutorial.

2. Materials

2.1. Software requirement

1) MolAICal : https://molaical.github.io (**Please use Development version!!!**)
2) NAMD: https://www.ks.uiuc.edu/Research/namd/

2.2. Example files

1) All the necessary tutorial files are downloaded from:
https://github.com/MolAICal/tutorials/tree/master/004-MMGBSA

3. Procedure

Go to the tutorial directory:
#> cd 004-MMGBSA

3.1. Extracting trajectory of protein in complex with ligand

#> vmd -dispdev text -psf "mpro.psf" -e stripDCD.vmd -args protein,or,resname,LIG "mpro.dcd" "complex" mpro.psf mpro.pdb

-args: it is the usage like the command “atomselect” of VMD software such as "atomselect top protein or resname LIG". Here, comma "," represents blank space " ". The script file “stripDCD.vmd” can be found in the directory “scripts” of MolAICal software.

It will generate complex.psf, complex.pdb and complex.dcd. Turning on the parameters of “GBIS” and “sasa”. Open “complex.conf” and modify the appropriate parameters of red fonts as below:

```
structure           complex.psf
coordinates         complex.pdb
outputName          complex

paraTypeCharmm      on
parameters          par_all36_prot.prm
parameters          par_all36_cgenff.prm
parameters          ligand.str
parameters          toppar_water_ions.str
```

coorfile open dcd complex.dcd

Our tutorial is run by CPU. You can run it on GPU. Running NAMD command in Linux operating system as below:

#> namd2 +p3 complex.conf >& complex.log &

Where the symbol "&" assigns the command to run in the background on the Linux operating system. If NAMD runs on Windows operating system, the symbol "&" must be omitted. For instance:

#> namd2 +p3 complex.conf > complex.log

3.2. Extracting trajectory of protein only.

#> vmd -dispdev text -psf "mpro.psf" -e stripDCD.vmd -args protein "mpro.dcd" "protein" mpro.psf mpro.pdb

It will generate protein.psf, protein.pdb and protein.dcd. Open "protein.conf" and modify the appropriate parameters in the similar way of "complex.conf"

Our tutorial is run by CPU. You can run it on GPU. Running NAMD command in Linux operating system as below:

#> namd2 +p3 protein.conf >& protein.log &

3.3. Extracting trajectory of ligand only.

#> vmd -dispdev text -psf "mpro.psf" -e stripDCD.vmd -args resname,LIG "mpro.dcd" "ligand" mpro.psf mpro.pdb

It will generate ligand.psf, ligand.pdb and ligand.dcd. Open "ligand.conf" and modify the appropriate parameters in the similar way of "complex.conf"

Our tutorial is run by CPU. You can run it on GPU. Running NAMD command in Linux operating system as below:

#> namd2 +p3 ligand.conf >& ligand.log &

3.4. Calculating MM/GBSA by MolAICal

#> molaical.exe -mmgbsa -c complex.log -r protein.log -l ligand.log

The output contains the binding free energy △G as below:

---

delta E(internal): -0
delta E(electrostatic) + deltaG(sol): 7.7029
delta E(VDW): -44.4361
delta G binding: -36.7332 +/- 3.4202 (kcal/mol)

3.5. Decomposing the free energy contributions of a per-residue

If the users want to use MolAICal to decompose the free energy contributions of a per-residue, it can draw lessons from the above steps. For example, the residue M165 of SARS-CoV-2 Mpro is reported to interact with ligand N3. So the residue M165 is chosen as an example. First of all, change the console into the "004-MMGBSA\Decompose" folder:

#> cd 004-MMGBSA\Decompose

3.5.1. Extracting trajectory of an appointed residue in complex with ligand

#> vmd -dispdev text -psf "../mpro.psf" -e ../stripDCD.vmd -args protein,and,resid,165,or,resname,LIG "../mpro.dcd" "res-lig" ../mpro.psf ../mpro.pdb

-args: it is the usage like the command "atomselect" of VMD software such as "atomselect top protein or resname LIG". Here, comma "," represents blank space " ". The script file "stripDCD.vmd" can be found in the directory "scripts" of MolAICal software.

It will generate res-lig.psf, res-lig.pdb and res-lig.dcd. Open "res-lig.conf" and modify the appropriate parameters in the similar way of "complex.conf"

Our tutorial is run by CPU. You can run it on GPU. Running NAMD command in Linux operating system as below:

#> namd2 +p3 res-lig.conf >& res-lig.log &

3.5.2. Extracting trajectory of an appointed residue only

#> vmd -dispdev text -psf "../mpro.psf" -e ../stripDCD.vmd -args protein,and,resid,165 "../mpro.dcd" "res" ../mpro.psf ../mpro.pdb

It will generate res.psf, res.pdb and res.dcd. Open "res.conf" and modify the appropriate parameters in the similar way of "complex.conf"

Our tutorial is run by CPU. You can run it on GPU. Running NAMD command in Linux operating system as below:

#> namd2 +p3 res.conf >& res.log &

3.5.3. Extracting trajectory of ligand only

#> vmd -dispdev text -psf "../mpro.psf" -e ../stripDCD.vmd -args resname,LIG "../mpro.dcd" "lig" ../mpro.psf ../mpro.pdb

It will generate lig.psf, lig.pdb and lig.dcd. Open "lig.conf" and modify the appropriate parameters in the similar way of "complex.conf"

Our tutorial is run by CPU. You can run it on GPU. Running NAMD command in Linux operating system as below:

#> namd2 +p3 lig.conf >& lig.log &

3.5.4. Calculating free energy contributions of a per-residue by MolAICal

#> molaical.exe -mmgbsa -c res-lig.log -r res.log -l lig.log

The output contains the binding free energy of a per-residue △G as below:

---

delta E(internal): 0

delta E(electrostatic) + deltaG(sol): -0.4691

delta E(VDW): -4.4319

delta G binding: -4.901 +/- 1.0524 (kcal/mol)

Note: the users can use the above similar method to calculate the free energy contribution of pairwise and per-residue by MolAICal.