**多配体vsREMD处理-trip13体系**

22210

小分子处理：

antechamber -i DCZ0415.pdb -fi pdb -o DCZ0415.gjf -fo gcrt

对DCZ0415.gjf 修改

%chk=DCZ0415

%nproc=16

#B3LYP/6-31G\* SCF=tight SCRF=SMD Test Pop=MK iop(6/33=2) iop(6/42=6) opt

g09 DCZ0415.gjf

antechamber -i DCZ0415.log -fi gout -o ligand.prep -fo prepi -c resp

parmchk -i ligand.prep -f prepi -o ligand.frcmod -a y ##得到小分子电荷参数

修改DCZ0415.pdb原子编号，每种元素从1依次往下。

H++处理蛋白，利用smina对接DCZ0415.pdb到另外四个位点，对结后构象用DS加H

D3pockets得到蛋白上的口袋，选中某个点后在pymol上：centeroffmass sele得到坐标；

smina --seed 0 -r 0.15\_80\_10\_pH7.4\_trip13.result.pdb -l DCZ0415.pdb -o cmpd\_smina.sdf --size\_x 25 --size\_y 25 --size\_z 25 --center\_x 13.868 --center\_y 301.286 --center\_z 215.305

利用packmol软件，在蛋白周围另外增加10个小分子：

./packmol < input.inp

tolerance 2.0 filetype pdb

output protein-s.pdb

structure protein.pdb

 number 1

 fixed 0. 0. 0. 0. 0. 0.

 centerofmass

end structure

structure DCZ0415.pdb

 number 10

 inside box -25 -25 -25 25. 25. 25.

end structure

sed -i '/N1 MOL/i\TER' protein-s.pdb

通过VMD在调整这10个小分子的位置，后保存。sed -i '/N1 MOL/i\TER' protein-s.pdb

用tleap处理生成蛋白-配体参数

tleap -s -f teap.in

source oldff/leaprc.ff14SB

source leaprc.gaff

loadAmberParams /home/jawang/software/amber18/dat/leap/parm/frcmod.ions234lm\_1264\_tip3p

loadAmberParams frcmod.ionsjc\_tip3p

loadamberparams ligand.frcmod

pro=loadamberprep ligand.prep

pro=loadpdb protein-vmd.pdb

saveamberparm pro protein.prmtop protein.inpcrd

addions pro Na+ 63

solvatebox pro TIP3PBOX 8

saveamberparm pro complex.prmtop complex.inpcrd

quit

用amber18的parmed模块将AMBER参数转成gromacs；

python change.py

import parmed as pmd

amber = pmd.load\_file('complex.prmtop', 'complex.inpcrd')

# Save a GROMACS topology and GRO file

amber.save('topol.top')

amber.save('gromacs.gro')

# Save a CHARMM PSF and crd file

amber.save('charmm.psf')

amber.save('charmm.crd')

vi topol.top

:1,$s/WAT/SOL/g

:1,$s/system1/Protein/g

:1,$s/Na+/NA /g

再添加行,在适合位置

; Include Position restraint file

#ifdef POSRES

#include "posre.itp"

#endif

gmx\_mpi make\_ndx -f gromacs.gro -o index.ndx ##生成protein\_MOL

gmx\_mpi genrestr -f gromacs.gro -n index.ndx -o posre.itp

vi gromacs.gro

:1,$s/WAT/SOL/g

:1,$s/Na+/NA /g

gmx\_mpi grompp -f em.mdp -p topol.top -c gromacs.gro -o em.tpr -maxwarn 1

gmx\_mpi mdrun -ntomp 32 -v -deffnm em

gmx\_mpi grompp -f npt.mdp -c em.gro -p topol.top -o npt.tpr -maxwarn 1

gmx\_mpi mdrun -ntomp 32 -v -deffnm npt (输出文件npt.gro)

## 副本准备

<http://folding.bmc.uu.se/remd/> 预估副本数目

md.mdp 文件需要注意是protein\_mol 能量组

## vsREMD模拟

for i in `seq 0 15`; do gmx\_mpi grompp -f md$i.mdp -c npt.gro -p topol.top -o md$i.tpr -maxwarn 1 -n index.ndx;done

mpirun -np 24 gmx\_mpi mdrun -v -deffnm md -replex 1000 -multi 24

**分析数据**

1. 将轨迹拆分成多个蛋白+单配体轨迹

gmx\_mpi make\_ndx -f md0.part0001.gro -o index.ndx ##将index.ndx文件加入一项[center] 和[protein\_mol]

gmx\_mpi trjconv -f md0.xtc -s md0.tpr -pbc mol -ur compact -center -o md0-ligand1.pdb -n index1.ndx

1. 分析蛋白-配体1
2. 分析配体1与蛋白残基的作用图谱，了解配体主要聚集在蛋白质的哪个区域##

sh do.sh

cpptraj=$AMBERHOME/bin/cpptraj

for s in `seq 0 50`; do

 j=$[$s\*1000]

 q=$[$j+1]

 m=$[$s+1]

 k=$[$m\*1000]

 $cpptraj <<\_EOF

parm ../md0-ligand3-ref.pdb

trajin ../md0-ligand3.pdb ${q} ${k} 1

trajout md0-ligand3-${s}.pdb

\_EOF

 sed -i '/CRYST1/d' md0-ligand3-${s}.pdb

 for i in `seq 0 999`;do

 j1=$[$i\*6521]

 k1=$[$j1+6521]

 m1=$[$j1+1]

 sed -n ''${m1}','${k1}'p' md0-ligand3-${s}.pdb > ${i}.pdb

 $cpptraj <<\_EOF

parm ${i}.pdb

reference ${i}.pdb

trajin ${i}.pdb

strip !(@6471-6517<@4.5)

strip @H\*

strip :MOL

trajout native${i}.pdb

\_EOF

 cat native${i}.pdb >> ../all-3.pdb

 done

 rm \*.pdb

done

sed -i '/MODEL/d' all-ligand1.pdb

sed -i '/TER/d' all-ligand1.pdb

sed -i '/ENDMDL/d' all-ligand1.pdb

cat all-ligand1.pdb |awk '{print($4,$5,$6)}' > ligand1.dat

sed -i 's/ /\_/g' ligand1.dat

uniq ligand1.dat >ligand1-u.dat

vi ligand1-u.dat ## :%s/$/x/

for i in `cat mode-u.dat`; do grep "$i" ligand1-u.dat|wc -l >> ligand1-map.dat;done

cat ligand1-map.dat|awk '{sum+=$1} END {print "Average = ", sum}'

cat ligand1-map.dat|awk '{print($1/500)}' > ligand1-map-1.dat

paste mode-u.dat ligand1-map-1.dat |awk '{print($1,$2)}' > ligand1-map-2.dat

for i in `cat ligandall-map.dat`;do grep "$i" ligand12-map-2.dat| awk '{print($2)}' >> ligand12-map-bfactor.dat;done

2）分析配体1的构象分布自由能图景

gmx\_mpi distance -f md0.xtc -s md0.tpr -select 'com of resnr 165 to 167 plus com of resnr 405' -oall atp-ligand1.xvg

gmx\_mpi rms -f md0-ligand1.pdb -s md0.tpr -o rms-ligand1.xvg -n index1.ndx ##叠合蛋白，计算配体RMSD

for i in `seq 1 15`;do sed '1,16d' atp-ligand$i.xvg > atp-ligand$i.dat;done

for i in `seq 2 8`;do sed '1,17d' rms-ligand$i.xvg > rms-ligand$i.dat;done

for i in `seq 3 15`;do paste rms-ligand$i.dat atp-ligand$i.dat |awk '{print($2,$4)}' > input$i.dat;done

./a.out 50001 0.15 0.15

提取聚类构象