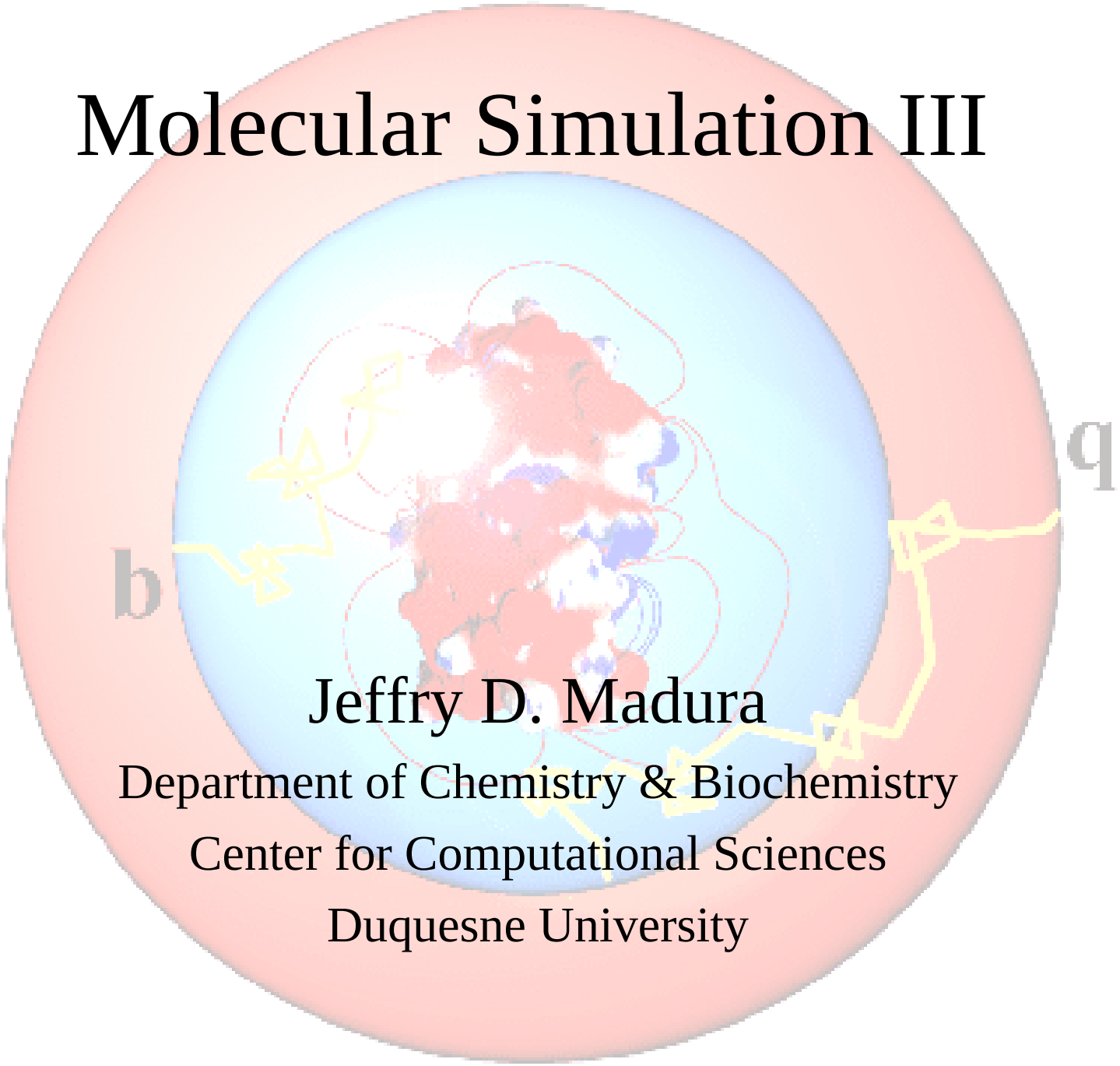
Molecular Simulation III



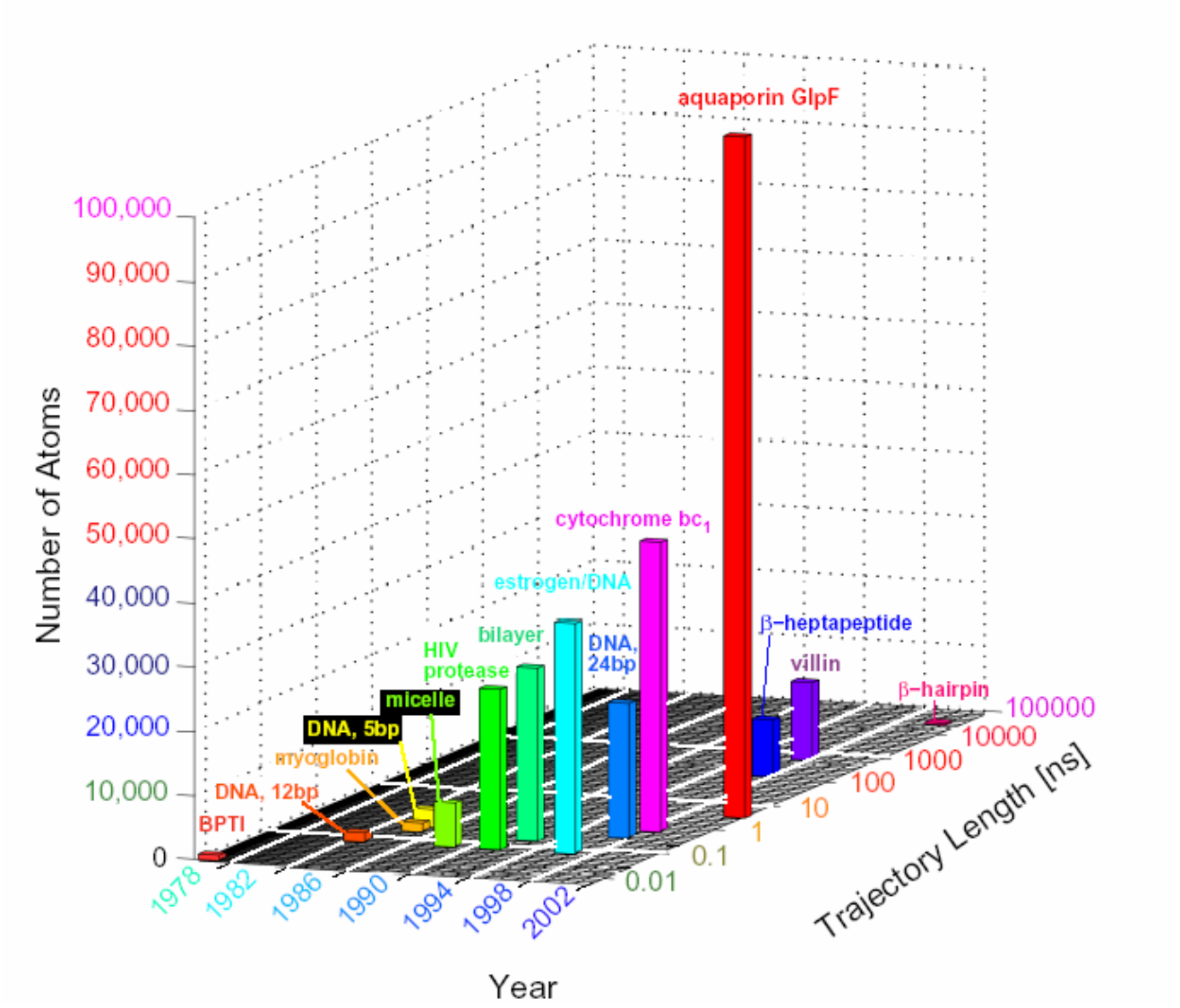
Jeffry D. Madura

Department of Chemistry & Biochemistry

Center for Computational Sciences

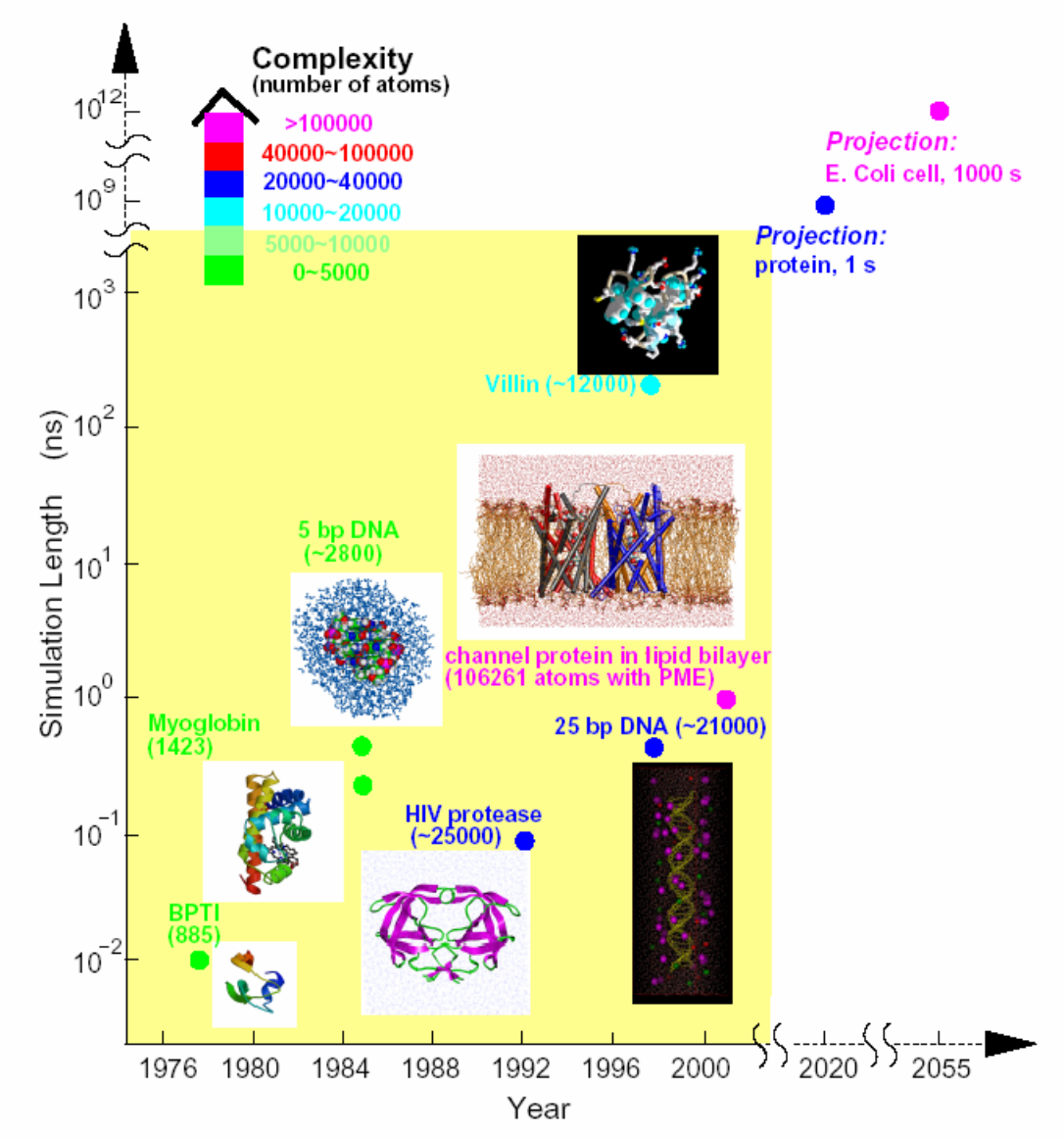
Duquesne University

Time and Length Scales



Tamar Schlick's Biomolecular Structure and Modeling

Simulation Lengths and Complexity

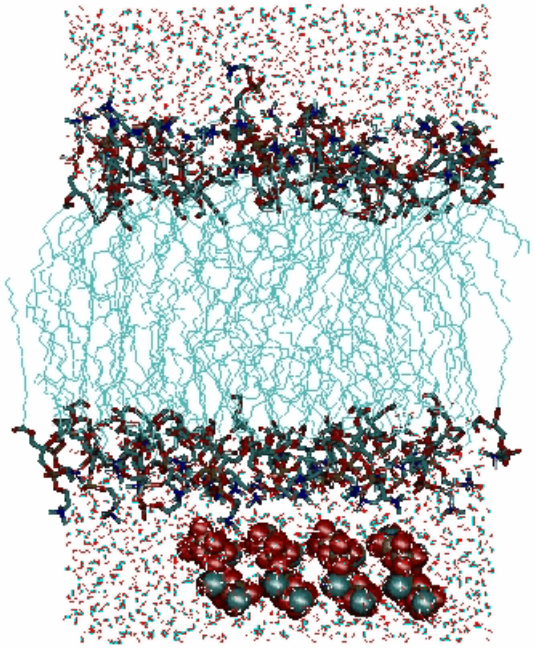


Tamar Schlick's Biomolecular Structure and Modeling

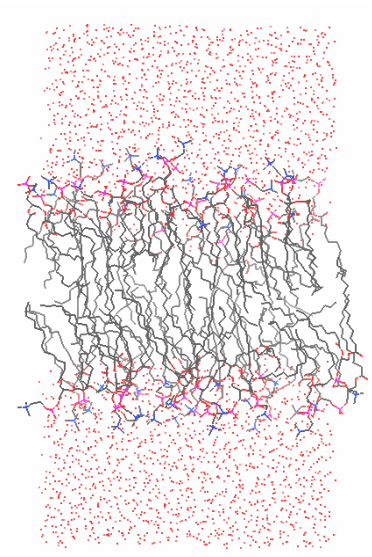
Molecular Dynamics

Crystal-Phospholipid Bilayer Interactions

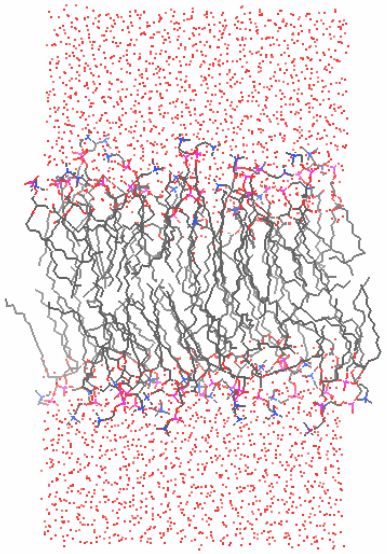
- Pseudogout (human inflamatory disease) caused by presence of *in vivo* crystals of calcium pyrophosphate dihydrate (CPPD).
- Molecular aspect of *in vivo* crystal induced inflammation is unknown
- Rupture of the lysosome phospholipid membrane is a commonly accepted mechanism of inflammation.
- Important to elucidate the nature of crystal-phospholipid bilayer interactions
- The knowledge will aid in developing inhibitors to diminish the adhesion of CPPD to membranes



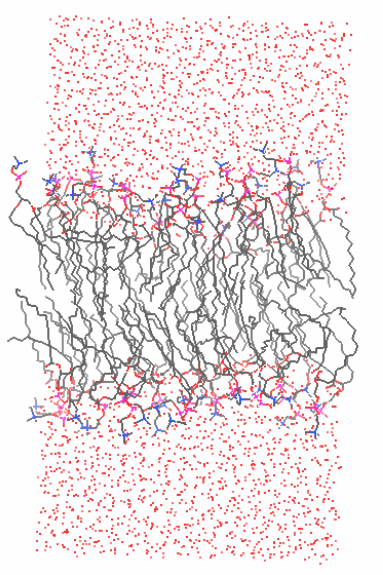
Solvated DMPC Bilayer in Absence and Presence of CPPD Crystal



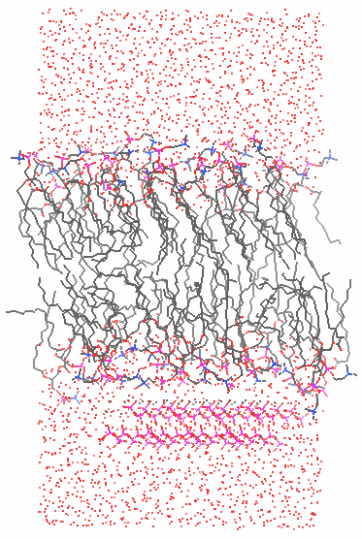
200 ps

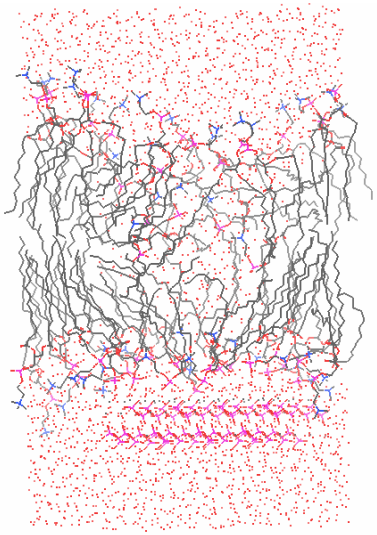


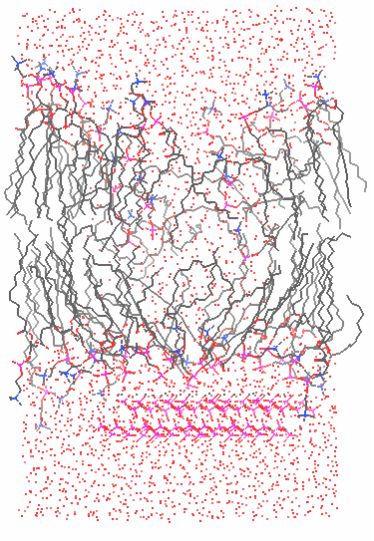
400 ps



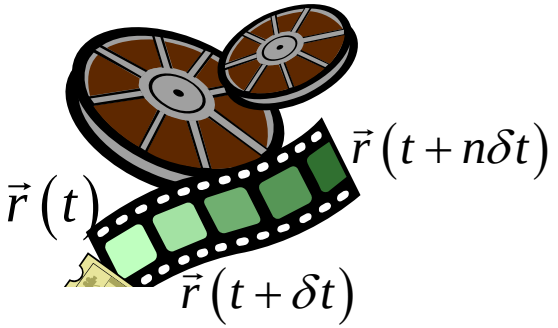
600 ps







MD Review



- Molecular dynamics is a numerical integration of the classical equations of motion

$$\vec{F} = m\vec{a} = m\frac{d^2\vec{x}}{dt^2}$$

- assuming conservative forces….

$$\vec{F} = -\nabla\vec{U}$$

- …the integrated equations of motion become

$$\vec{r}(t+\delta t) = \vec{r}(t) - \vec{r}(t-\delta t) + \frac{1}{m}\vec{F}(t)\delta t^2$$

Topology

```
*>>>>>>>>CHARMM22 All-Hydrogen Topology File for Proteins <<<<<<
*>>>>>>>>>>>>>>>>>>>> August 1999 <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
*>>>>>>> Direct comments to Alexander D. MacKerell Jr. <<<<<<<<<
*>>>>>> 410-706-7442 or email: alex,mmiris.ab.umd.edu  <<<<<<<<<
*
27  1

!
! references
!
!PROTEINS
!
!MacKerell, Jr., A. D.; Bashford, D.; Bellott, M.; Dunbrack Jr., R.L.;
!Evanseck, J.D.; Field, M.J.; Fischer, S.; Gao, J.; Guo, H.; Ha, S.;
!Joseph-McCarthy, D.; Kuchnir, L.; Kuczera, K.; Lau, F.T.K.; Mattos,
!C.; Michnick, S.; Ngo, T.; Nguyen, D.T.; Prodhom, B.; Reiher, III,
!W.E.; Roux, B.; Schlenkrich, M.; Smith, J.C.; Stote, R.; Straub, J.;
!Watanabe, M.; Wiorkiewicz-Kuczera, J.; Yin, D.; Karplus, M.  All-atom
!empirical potential for molecular modeling and dynamics Studies of
!proteins.  Journal of Physical Chemistry B, 1998, 102, 3586-3616.
!

MASS     1 H      1.00800 H ! polar H
MASS     2 HC     1.00800 H ! N-ter H
MASS     3 HA     1.00800 H ! nonpolar H
MASS     4 HT     1.00800 H ! TIPS3P WATER HYDROGEN
MASS     5 HP     1.00800 H ! aromatic H
MASS     6 HB     1.00800 H ! backbone H
MASS     7 HR1    1.00800 H ! his he1, (+) his HG,HD2
MASS     8 HR2    1.00800 H ! (+) his HE1
MASS     9 HR3    1.00800 H ! neutral his HG, HD2
MASS    10 HS     1.00800 H ! thiol hydrogen
MASS    11 HE1    1.00800 H ! for alkene; RHC=CR
MASS    12 HE2    1.00800 H ! for alkene; H2C=CR
```

Topology

```
MASS    20 C     12.01100 C ! carbonyl C, peptide backbone
MASS    21 CA    12.01100 C ! aromatic C
MASS    22 CT1   12.01100 C ! aliphatic sp3 C for CH
MASS    23 CT2   12.01100 C ! aliphatic sp3 C for CH2
MASS    24 CT3   12.01100 C ! aliphatic sp3 C for CH3
MASS    25 CPH1  12.01100 C ! his CG and CD2 carbons
MASS    26 CPH2  12.01100 C ! his CE1 carbon
MASS    27 CPT   12.01100 C ! trp C between rings
MASS    28 CY    12.01100 C ! TRP C in pyrrole ring
MASS    29 CP1   12.01100 C ! tetrahedral C (proline CA)
MASS    30 CP2   12.01100 C ! tetrahedral C (proline CB/CG)
MASS    31 CP3   12.01100 C ! tetrahedral C (proline CD)
MASS    32 CC    12.01100 C ! carbonyl C, asn,asp,gln,glu,cter,ct2
MASS    33 CD    12.01100 C ! carbonyl C, pres aspp,glup,ct1
MASS    34 CPA   12.01100 C ! heme alpha-C
MASS    35 CPB   12.01100 C ! heme beta-C
MASS    36 CPM   12.01100 C ! heme meso-C
MASS    37 CM    12.01100 C ! heme CO carbon
MASS    38 CS    12.01100 C ! thiolate carbon
MASS    39 CE1   12.01100 C ! for alkene; RHC=CR
MASS    40 CE2   12.01100 C ! for alkene; H2C=CR
MASS    50 N     14.00700 N ! proline N
MASS    51 NR1   14.00700 N ! neutral his protonated ring nitrogen
MASS    52 NR2   14.00700 N ! neutral his unprotonated ring nitrogen
MASS    53 NR3   14.00700 N ! charged his ring nitrogen
MASS    54 NH1   14.00700 N ! peptide nitrogen
MASS    55 NH2   14.00700 N ! amide nitrogen
MASS    56 NH3   14.00700 N ! ammonium nitrogen
MASS    57 NC2   14.00700 N ! guanidinium nitroogen
MASS    58 NY    14.00700 N ! TRP N in pyrrole ring
MASS    59 NP    14.00700 N ! Proline ring NH2+ (N-terminal)
MASS    60 NPH   14.00700 N ! heme pyrrole N
MASS    70 O     15.99900 O ! carbonyl oxygen
MASS    71 OB    15.99900 O ! carbonyl oxygen in acetic acid
MASS    72 OC    15.99900 O ! carboxylate oxygen
MASS    73 OH1   15.99900 O ! hydroxyl oxygen
MASS    74 OS    15.99940 O ! ester oxygen
MASS    75 OT    15.99940 O ! TIPS3P WATER OXYGEN
MASS    76 OM    15.99900 O ! heme CO/O2 oxygen
MASS    81 S     32.06000 S ! sulphur
MASS    82 SM    32.06000 S ! sulfur C-S-S-C type
MASS    83 SS    32.06000 S ! thiolate sulfur
MASS    85 HE     4.00260 HE ! helium
MASS    86 NE    20.17970 NE ! neon
MASS    90 CAL   40.08000 CA ! calcium 2+
MASS    91 ZN    65.37000 ZN ! zinc (II) cation
MASS    92 FE    55.84700 Fe ! heme iron 56
MASS    99 DUM    0.00000 H ! dummy atom
```

Topology (butane)

```
Resi BUTA        0.00 ! butane, S. Fischer
Group                                        
Atom  h11 ha     0.09 !  H11   H21 H31    H41
Atom  h12 ha     0.09 !    \    |   |     /  
Atom  h13 ha     0.09 ! H12-C1--C2--C3--C4-H42
Atom  c1  ct3   -0.27 !    /    |   |     \  
Group                 !  H13   H22 H33    H43
Atom  h21 ha     0.09                        
Atom  h22 ha     0.09                        
Atom  c2  ct2   -0.18                        
Group                                        
Atom  h31 ha     0.09                        
Atom  h32 ha     0.09                        
atom  c3  ct2   -0.18                        
Group                                        
atom  h41 ha     0.09                        
atom  h42 ha     0.09                        
atom  h43 ha     0.09                        
atom  c4  ct3   -0.27                        
Bond h11 c1  h12 c1  h13 c1  c1 c2
Bond h21 c2  h22 c2  c2  c3
Bond h31 c3  h32 c3  c3  c4
Bond h41 c4  h42 c4  h43 c4
```

```
ic  h11 c1 c2 c3  0.00  0.00    0.0  0.00 0.00
ic  h11 c1 c2 h21 0.00  0.00  120.0  0.00 0.00
ic  h11 c1 c2 h22 0.00  0.00  240.0  0.00 0.00
ic  h12 c1 c2 c3  0.00  0.00  120.0  0.00 0.00
ic  h13 c1 c2 c3  0.00  0.00  240.0  0.00 0.00
ic  c1  c2 c3 c4  0.00  0.00    0.0  0.00 0.00
ic  c1  c2 c3 h31 0.00  0.00  120.0  0.00 0.00
ic  c1  c2 c3 h32 0.00  0.00  240.0  0.00 0.00
ic  h21 c2 c3 c4  0.00  0.00  120.0  0.00 0.00
ic  h22 c2 c3 c4  0.00  0.00  240.0  0.00 0.00
ic  c2  c3 c4 h41 0.00  0.00    0.0  0.00 0.00
ic  c2  c3 c4 h42 0.00  0.00  120.0  0.00 0.00
ic  c2  c3 c4 h43 0.00  0.00  240.0  0.00 0.00
ic  h31 c3 c4 h43 0.00  0.00  120.0  0.00 0.00
ic  h32 c3 c4 h43 0.00  0.00  240.0  0.00 0.00
```

Topology

```
RESI ALA          0.00
GROUP
ATOM N    NH1    -0.47  !     |
ATOM HN   H       0.31  !  HN-N
ATOM CA   CT1     0.07  !     |     HB1
ATOM HA   HB      0.09  !     |    /
GROUP                   !  HA-CA--CB-HB2
ATOM CB   CT3    -0.27  !     |    \
ATOM HB1  HA      0.09  !     |     HB3
ATOM HB2  HA      0.09  !   O=C
ATOM HB3  HA      0.09  !     |
GROUP                   !
ATOM C    C       0.51
ATOM O    O      -0.51
BOND CB CA  N  HN  N  CA
BOND C  CA  C  +N  CA HA  CB HB1  CB HB2  CB HB3
DOUBLE O  C
IMPR N -C CA HN  C CA +N O
DONOR HN N
ACCEPTOR O C
IC -C   CA   *N   HN    1.3551 126.4900  180.0000 115.4200  0.9996
IC -C   N    CA   C     1.3551 126.4900  180.0000 114.4400  1.5390
IC N    CA   C    +N    1.4592 114.4400  180.0000 116.8400  1.3558
IC +N   CA   *C   O     1.3558 116.8400  180.0000 122.5200  1.2297
IC CA   C    +N   +CA   1.5390 116.8400  180.0000 126.7700  1.4613
IC N    C    *CA  CB    1.4592 114.4400  123.2300 111.0900  1.5461
IC N    C    *CA  HA    1.4592 114.4400 -120.4500 106.3900  1.0840
IC C    CA   CB   HB1   1.5390 111.0900  177.2500 109.6000  1.1109
IC HB1  CA   *CB  HB2   1.1109 109.6000  119.1300 111.0500  1.1119
IC HB1  CA   *CB  HB3   1.1109 109.6000 -119.5800 111.6100  1.1114
```

Parameters (bonds)

```
*>>>> CHARMM22 All-Hydrogen Parameter File for Proteins <<<<<<<<<<
*>>>>>>>>>>>>>>>>>>>>>> August 1999 <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
*>>>>>>> Direct comments to Alexander D. MacKerell Jr. <<<<<<<<<
*>>>>>> 410-706-7442 or email: alex,mmiris.ab.umd.edu  <<<<<<<<<
*
!PROTEINS
!
!MacKerell, Jr., A. D.; Bashford, D.; Bellott, M.; Dunbrack Jr., R.L.;
!Evanseck, J.D.; Field, M.J.; Fischer, S.; Gao, J.; Guo, H.; Ha, S.;
!Joseph-McCarthy, D.; Kuchnir, L.; Kuczera, K.; Lau, F.T.K.; Mattos,
!C.; Michnick, S.; Ngo, T.; Nguyen, D.T.; Prodhom, B.; Reiher, III,
!W.E.; Roux, B.; Schlenkrich, M.; Smith, J.C.; Stote, R.; Straub, J.;
!Watanabe, M.; Wiorkiewicz-Kuczera, J.; Yin, D.; Karplus, M.  All-atom
!empirical potential for molecular modeling and dynamics Studies of
!proteins.  Journal of Physical Chemistry B, 1998, 102, 3586-3616.
!
BONDS
!
!V(bond) = Kb(b - b0)**2
!
!Kb: kcal/mole/A**2
!b0: A
!
!atom type Kb          b0
!
C    C     600.000     1.3350 ! ALLOW ARO HEM
            ! Heme vinyl substituent (KK, from propene (JCS))
CA   CA    305.000     1.3750 ! ALLOW   ARO
            ! benzene, JES 8/25/89
CE1  CE1   440.000     1.3400   !
                          ! for butene; from propene, yin/adm jr., 12/95
CE1  CE2   500.000     1.3420   !
                          ! for propene, yin/adm jr., 12/95
CE1  CT2   365.000     1.5020   !
                          ! for butene; from propene, yin/adm jr., 12/95
```

Parameters (angles)

```
ANGLES
!
!V(angle) = Ktheta(Theta - Theta0)**2
!
!V(Urey-Bradley) = Kub(S - S0)**2
!
!Ktheta: kcal/mole/rad**2
!Theta0: degrees
!Kub: kcal/mole/A**2 (Urey-Bradley)
!S0: A
!
!atom types     Ktheta    Theta0   Kub     S0
!
CA   CA   CA    40.000    120.00   35.00   2.41620 ! ALLOW   ARO
            ! JES 8/25/89
CE1  CE1  CT3    48.00    123.50   !
                          ! for 2-butene, yin/adm jr., 12/95
CE1  CT2  CT3    32.00    112.20   !
                          ! for 1-butene; from propene, yin/adm jr., 12/95
CE2  CE1  CT2    48.00    126.00   !
                          ! for 1-butene; from propene, yin/adm jr., 12/95
CE2  CE1  CT3    47.00    125.20   !
                          ! for propene, yin/adm jr., 12/95
CP1  N    C      60.000   117.0000 ! ALLOW PRO
            ! 6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93
CP2  CP1  C      52.000   112.3000 ! ALLOW PRO
            ! 6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93
CP2  CP1  CC     52.000   112.3000 ! ALLOW PRO
            ! 6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93
CP2  CP1  CD     50.000   112.3000 ! ALLOW PRO PEP
            ! 6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93
CP2  CP2  CP1    70.000   108.5000 ! ALLOW PRO
            ! 6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93
CP3  CP2  CP2    70.000   108.5000 ! ALLOW PRO
            ! 6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93
CP3  N    C      60.000   117.0000 ! ALLOW PRO
            ! 6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93
CP3  N    CP1   100.000   114.2000 ! ALLOW PRO
            ! 6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93
```

Parameters (dihedrals)

```
DIHEDRALS
!
!V(dihedral) = Kchi(1 + cos(n(chi) - delta))
!
!Kchi: kcal/mole
!n: multiplicity
!delta: degrees
!
!atom types             Kchi    n   delta
!
C    CT1  NH1  C       0.2000  1   180.00 ! ALLOW PEP
             ! ala dipeptide update for new C VDW Rmin, adm jr., 3/3/93c
C    CT2  NH1  C       0.2000  1   180.00 ! ALLOW PEP
             ! ala dipeptide update for new C VDW Rmin, adm jr., 3/3/93c
C    N    CP1  C       0.8000  3     0.00 ! ALLOW PRO PEP
             ! 6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93
CA   CA   CA   CA      3.1000  2   180.00 ! ALLOW   ARO
             ! JES 8/25/89
CA   CPT  CPT  CA      3.1000  2   180.00 ! ALLOW   ARO
             ! JWK 05/14/91 fit to indole
CA   CT2  CT1  C       0.0400  3     0.00 ! ALLOW   ARO
             ! 2.7 kcal/mole CH3 rot in ethylbenzene, adm jr, 3/7/92
CA   CY   CPT  CA      3.0000  2   180.00 ! ALLOW   ARO
             ! JWK 09/05/89
CA   NY   CPT  CA      3.0000  2   180.00 ! ALLOW   ARO
             ! JWK 05/14/91 fit to indole
CC   CP1  N    C       0.8000  3     0.00 ! ALLOW PRO PEP
             ! 6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93
CC   CT1  CT2  CA      0.0400  3     0.00 ! ALLOW   ARO
             ! 2.7 kcal/mole CH3 rot in ethylbenzene, adm jr, 3/7/92
CC   CT1  NH1  C       0.2000  1   180.00 ! ALLOW PEP POL
             ! ala dipeptide update for new C VDW Rmin, adm jr., 3/3/93c
CC   CT2  NH1  C       0.2000  1   180.00 ! ALLOW PEP POL
             ! Alanine dipeptide; NMA; acetate; etc. adm jr., 3/3/93c
CD   CP1  N    C       0.0000  1   180.00 ! ALLOW PRO PEP
             ! 6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93
```

Parameters (improper)

```
IMPROPER
!
!V(improper) = Kpsi(psi - psi0)**2
!
!Kpsi: kcal/mole/rad**2
!psi0: degrees
!note that the second column of numbers (0) is ignored
!
!atom types          Kpsi                   psi0
!
CPB  CPA  NPH  CPA    20.8000         0      0.0000 ! ALLOW HEM
            ! Heme (6-liganded): porphyrin macrocycle (KK 05/13/91)
CPB  X    X    C      90.0000         0      0.0000 ! ALLOW HEM
            ! Heme (6-liganded): substituents (KK 05/13/91)
CT2  X    X    CPB    90.0000         0      0.0000 ! ALLOW HEM
            ! Heme (6-liganded): substituents (KK 05/13/91)
CT3  X    X    CPB    90.0000         0      0.0000 ! ALLOW HEM
            ! Heme (6-liganded): substituents (KK 05/13/91)
HA   C    C    HA     20.0000         0      0.0000 ! ALLOW   PEP POL ARO
            ! Heme vinyl substituent (KK, from propene (JCS))
HA   CPA  CPA  CPM    29.4000         0      0.0000 ! ALLOW HEM
            ! Heme (6-liganded): porphyrin macrocycle (KK 05/13/91)
HA   CPB  C    C      20.0000         0      0.0000 ! ALLOW HEM ARO
            ! Heme (6-liganded): substituents (KK 05/13/91)
HA   HA   C    C      20.0000         0    180.0000 ! ALLOW   PEP POL ARO
            ! Heme vinyl substituent (KK, from propene (JCS))
HE2  HE2  CE2  CE2     3.0            0      0.00   !
                           ! for ethene, yin/adm jr., 12/95
HR1  NR1  NR2  CPH2    0.5000         0      0.0000 ! ALLOW ARO
            ! his, adm jr., 7/05/90
HR1  NR2  NR1  CPH2    0.5000         0      0.0000 ! ALLOW ARO
            ! his, adm jr., 7/05/90
HR3  CPH1 NR1  CPH1    0.5000         0      0.0000 ! ALLOW ARO
            ! adm jr., 3/24/92, maintain old aliphatic H VDW params
HR3  CPH1 NR2  CPH1    0.5000         0      0.0000 ! ALLOW ARO
            ! adm jr., 3/24/92, maintain old aliphatic H VDW params
```

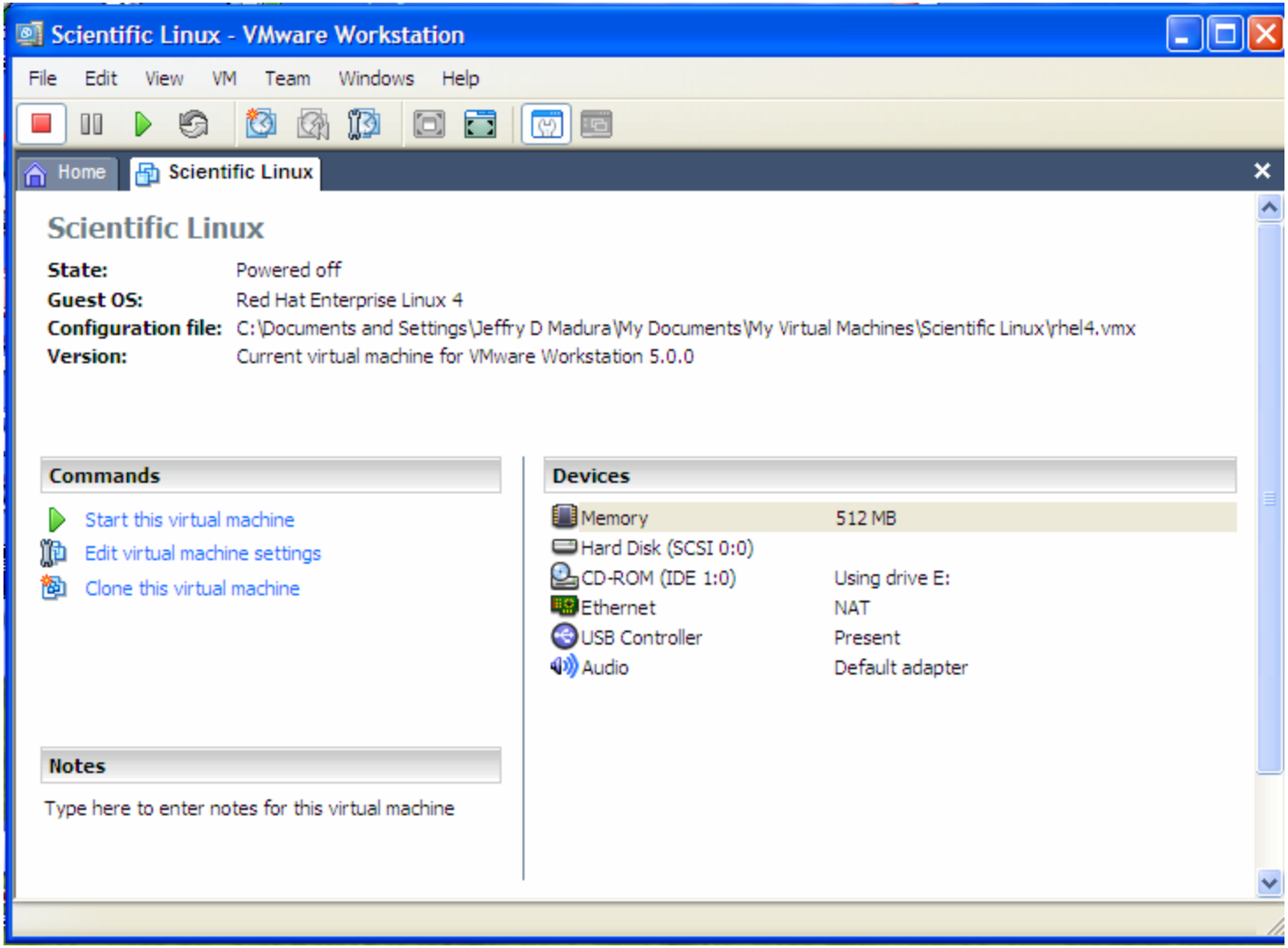
Parameters (nonbond)

```
NONBONDED nbxmod  5 atom cdiel shift vatom vdistance vswitch -
cutnb 14.0 ctofnb 12.0 ctonnb 10.0 eps 1.0 e14fac 1.0 wmin 1.5
            !adm jr., 5/08/91, suggested cutoff scheme
!
!V(Lennard-Jones) = Eps,i,j[(Rmin,i,j/ri,j)**12 - 2(Rmin,i,j/ri,j)**6]
!
!epsilon: kcal/mole, Eps,i,j = sqrt(eps,i * eps,j)
!Rmin/2: A, Rmin,i,j = Rmin/2,i + Rmin/2,j
!
!atom  ignored    epsilon      Rmin/2   ignored   eps,1-4       Rmin/2,1-4
!
C      0.000000  -0.110000     2.000000 ! ALLOW   PEP POL ARO
            ! NMA pure solvent, adm jr., 3/3/93
CA     0.000000  -0.070000     1.992400 ! ALLOW   ARO
            ! benzene (JES)
CC     0.000000  -0.070000     2.000000 ! ALLOW   PEP POL ARO
            ! adm jr. 3/3/92, acetic acid heat of solvation
CD     0.000000  -0.070000     2.000000 ! ALLOW  POL
            ! adm jr. 3/19/92, acetate a.i. and dH of solvation
CE1    0.000000  -0.068000     2.090000 !
                        ! for propene, yin/adm jr., 12/95
CE2    0.000000  -0.064000     2.080000 !
                        ! for ethene, yin/adm jr., 12/95
CM     0.000000  -0.110000     2.100000 ! ALLOW HEM
            ! Heme (6-liganded): CO ligand carbon (KK 05/13/91)
CP1    0.000000  -0.020000     2.275000   0.000000  -0.010000     1.900000 ! ALLOW   ALI
            ! alkane update, adm jr., 3/2/92
CP2    0.000000  -0.055000     2.175000   0.000000  -0.010000     1.900000 ! ALLOW   ALI
            ! alkane update, adm jr., 3/2/92
CP3    0.000000  -0.055000     2.175000   0.000000  -0.010000     1.900000 ! ALLOW   ALI
            ! alkane update, adm jr., 3/2/92
CPA    0.000000  -0.090000     1.800000 ! ALLOW HEM
            ! Heme (6-liganded): porphyrin macrocycle (KK 05/13/91)
```

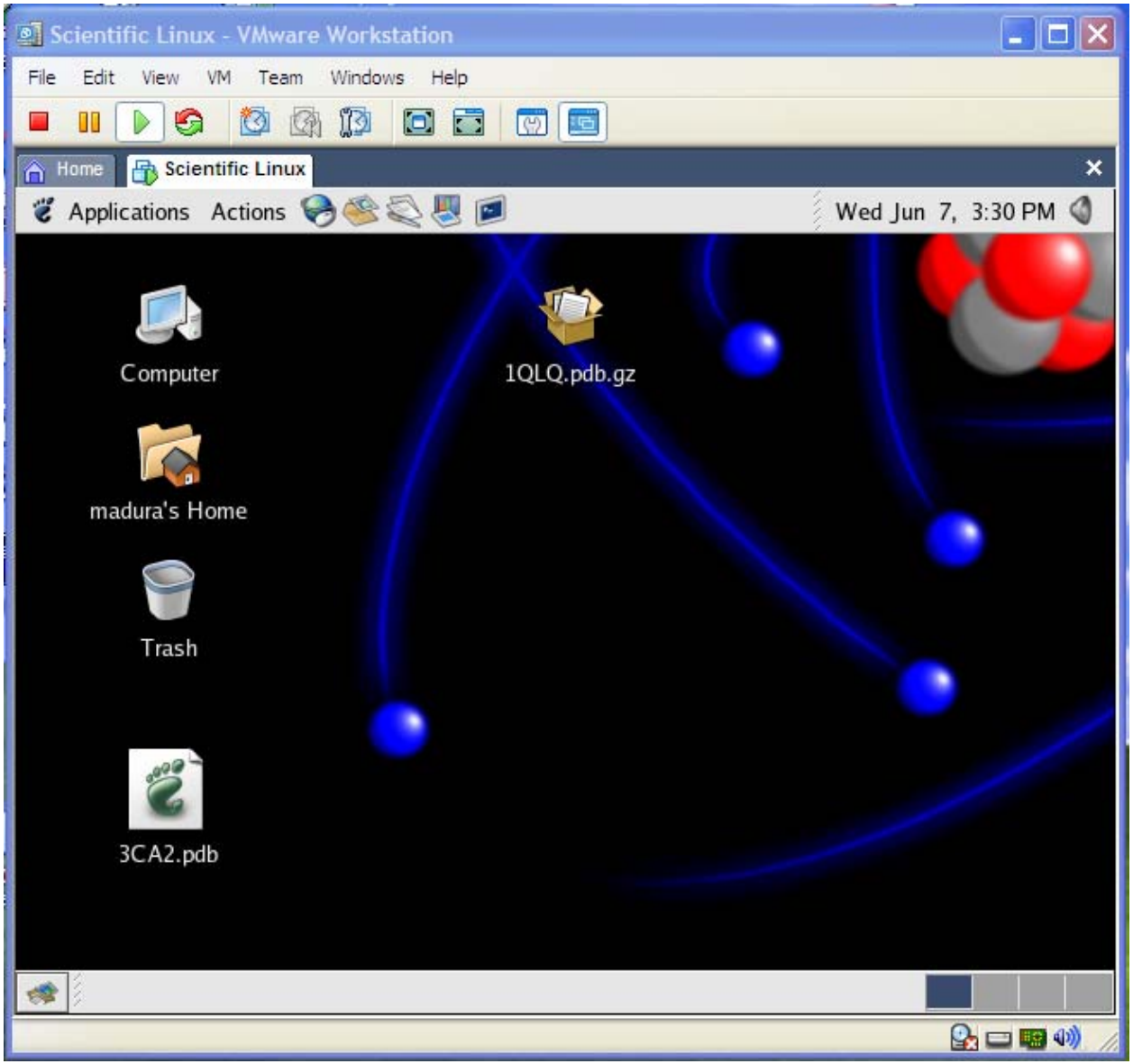
Step 1: Generate

```
* ryan newton
* 5/21/2004
* generate butane
*

! machine dependent parameters
PRNLEv 5
BOMLev -2

! set user specific parameters
set 1 top_all22_model.inp
set 2 par_all22_protnew.inp

! read the topology
open unit 9 read form name @1
read rtf card unit 9
close unit 9

! read the parameters
open unit 9 read form name @2
read para card unit 9
close unit 9

! read butane card from topology file
read sequence cards
* butane
*
1
BUTA

generate BUTA first none last none setup warn

! internal coordinate parameters
ic param
ic seed 1 C1 1 C2 1 C3

! place internal coordinates
ic build

!create hydrogens
hbuild

! print internal coordinates
print coor
ic print
coor stat

! minimize energy
mini sd nstep 50
mini nrap nstep 50
! create coordinate file
open unit 20 write form name butane.crd
write coor cards unit 20
* lipid all-hydrogen generated coordinates
* @1
* @2
*

!create psf file
open unit 20 write form name butane.psf
write psf cards unit 20
* lipid all-hydrogen psf
* @1
* @2
*
```

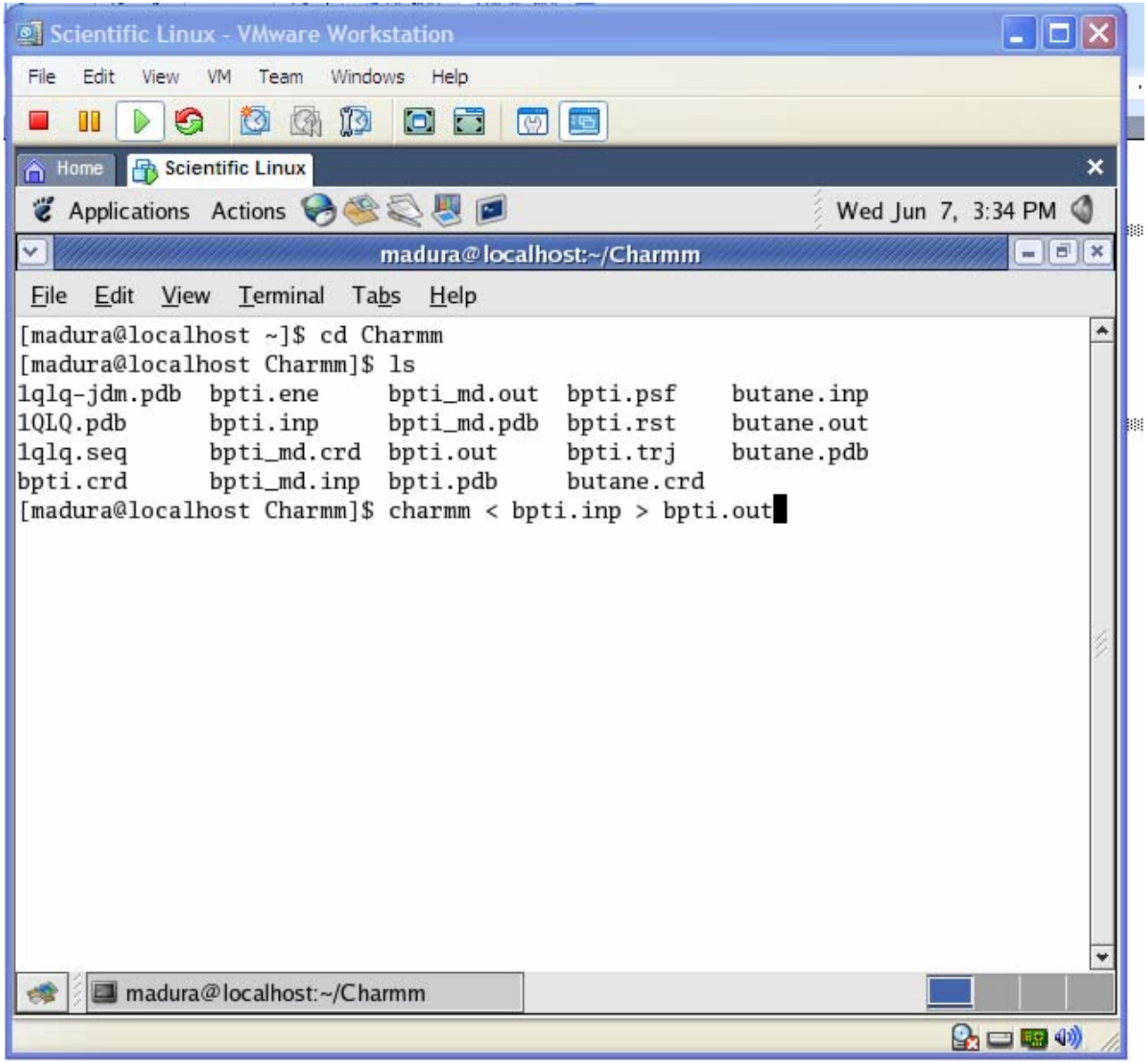
VMWARE


Scientific Linux - VMware Workstation
File Edit View VM Team Windows Help
Home
Scientific Linux
Scientific Linux
State: Powered off
Guest OS: Red Hat Enterprise Linux 4
Configuration file: C:\Documents and Settings\Jeffry D Madura\My Documents\My Virtual Machines\Scientific Linux\rhel4.vmx
Version: Current virtual machine for VMware Workstation 5.0.0
Commands
Start this virtual machine
Edit virtual machine settings
Clone this virtual machine
Devices
Memory 512 MB
Hard Disk (SCSI 0:0)
CD-ROM (IDE 1:0) Using drive E:
Ethernet NAT
USB Controller Present
Audio Default adapter
Notes
Type here to enter notes for this virtual machine

VMWARE

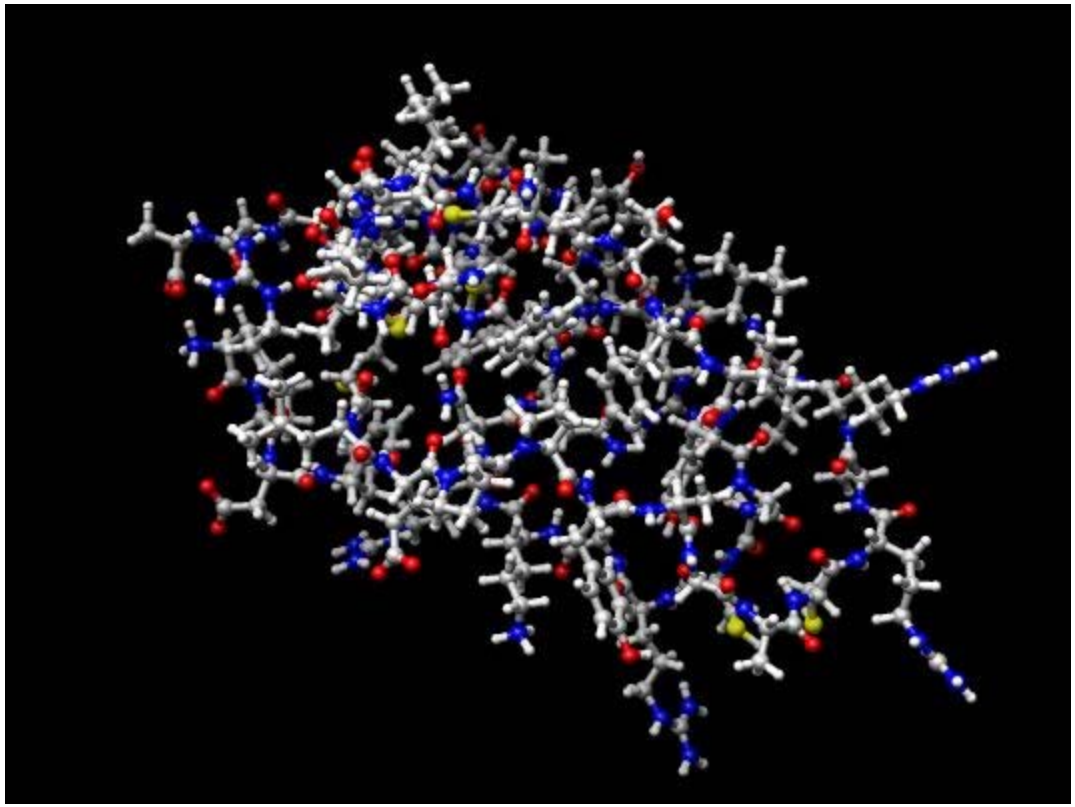

Scientific Linux - VMware Workstation
File Edit View VM Team Windows Help
Home
Scientific Linux
Applications Actions
Wed Jun 7, 3:30 PM
Computer
1QLQ.pdb.gz
madura's Home
Trash
3CA2.pdb

Running CHARMM



Molecular Dynamics of BPTI

- BPTI: Bovine Pancreatic Trypsin Inhibitor
  - Small protein of 58 amino acid residues
  - Protein used in first MD simulations



Dynamics Input

```
* * BPTI molecular dynamics
* 05/26/2006 jdm
*

! machine dependent parameters
PRNLEv 5
BOMLev -2

! set user specified parameters
set 1 ~/c32b1/toppar/top_all30_cheq_prot.inp
set 2 ~/c32b1/toppar/par_all30_cheq_prot.inp

! read the topology
open unit 9 read form name @1
read rtf card unit 9
close unit 9

! read the parameters
open unit 9 read form name @2
read para card unit 9
close unit 9

! read the sequence
read sequence cards
* bpti sequence from 1QLQ.pdb
*
58
ARG PRO ASP PHE CYS LEU GLU PRO PRO TYR ALA GLY ALA
CYS ARG ALA ARG ILE ILE ARG TYR PHE TYR ASN ALA LYS
ALA GLY LEU CYS GLN THR PHE VAL TYR GLY GLY CYS ARG
ALA LYS ARG ASN ASN PHE LYS SER ALA GLU ASP CYS LEU
ARG THR CYS GLY GLY ALA

generate BPTI first nter last cter setup warn

! read the minimized coordinates
open unit 9 read form name bpti.pdb
read coor pdb unit 9
close unit 9
```

Dynamics Input

```
! hold all X-H bonds fixed
shake bonh para

! open files for restart, trajectory, and energies
open unit 31 write form name bpti.rst
open unit 32 write unfo name bpti.trj
open unit 33 write form name bpti.ene

! molecular dynamics
dyna strt verlet nstep 5000 timestep 0.002 rdie -
   vswitch -
   iprfrq 100 ihtfrq 50 ieqfrq 0 inbrf1 -1 ihbfrq 0 echeck 999.0 -
   iunrea -1iunwri 31 iuncrd 32 iunvel -1 kunit 33 -
   nprint 50 nsavc 50 nsavv 50 -
   firstt 0.0 finalt 300.0 teminc 50 -
   twindh 10.0 twindl -10.0 -
   iasors 1 iasvel 1 ichecw 0
```

Dynamics Input

```
! create coordinate file
open unit 20 write form name bpti_md.crd
write coor cards unit 20
* bpti all hydrogen generated coordinates
* md run
* Topology file @1
* Parameter file @2
* Final energy ?ener
*
```

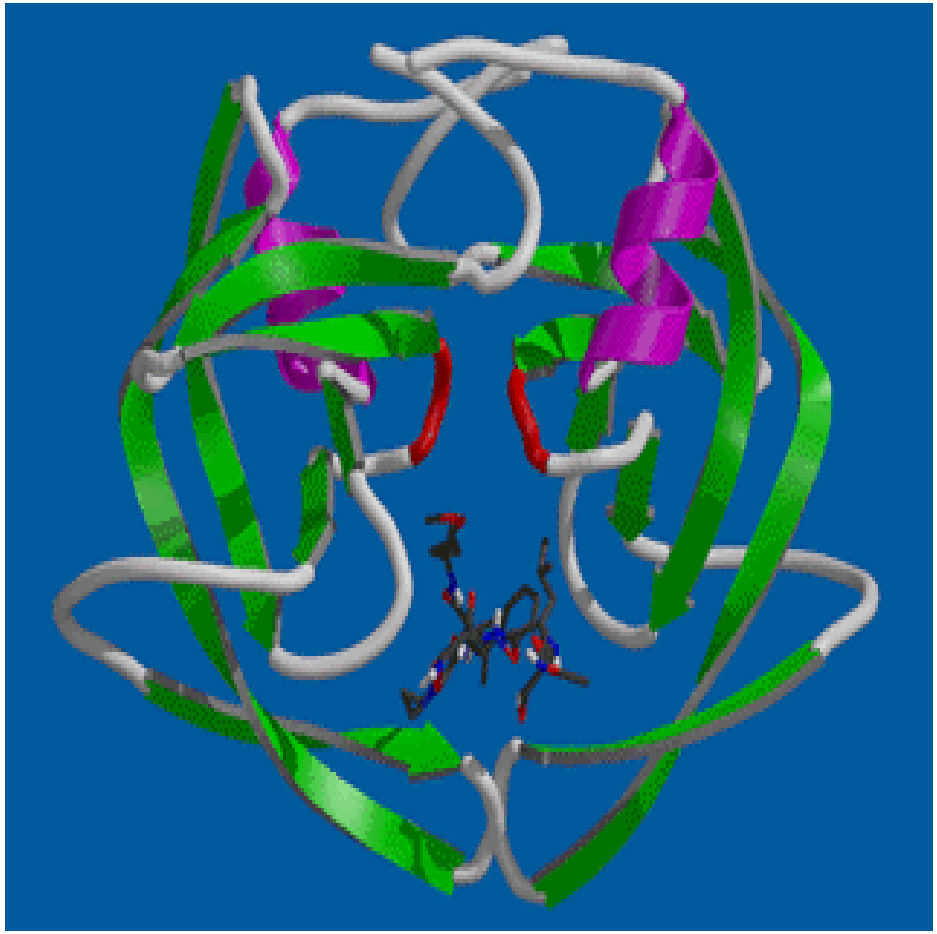
```
! write a charmm psf file
open write unit 18 card name bpti.psf
write psf unit 18 card
* bpti psf
*

close 18

! create coordinate file
open unit 20 write form name bpti_md.pdb
write coor pdb unit 20
* bpti all hydrogen generated coordinates
* md run
* Topology file @1
* Parameter file @2
* Final energy ?ener
*

stop
```

Dynamics Output

```
AVER DYN: Step     Time      TOTEner        TOTKe       ENERgy
   TEMPerature
AVER PROP:         GRMS      HFCTote        HFCKe       EHFCor
   VIRKe
AVER INTERN:      BONDs       ANGLes       UREY-b    DIHEdrals
   IMPRopers
AVER CROSS:       CMAPs
AVER EXTERN:    VDWaals         ELEC       HBONds          ASP
   USER
AVER PRESS:        VIRE         VIRI       PRESSE       PRESSI
   VOLUme
 ----------   ---------    ---------    ---------    ---------    -----
   ----
AVER>      100  9.60000   3554.94730    743.24070   2811.70660
   334.83951
AVER PROP>     19.53054   3563.73928    769.68781      8.79198
   865.43486
AVER INTERN>  169.89684    515.51136     54.58767    364.90914
   41.59984
AVER CROSS>  3176.17447
AVER EXTERN>  -77.20274  -1433.76999      0.00000      0.00000
   0.00000
AVER PRESS>     0.00000   -576.95658      0.00000      0.00000
   0.00000
 ----------   ---------    ---------    ---------    ---------    -----
```

Docking

Ligand-Receptor Docking



- Deals with **identification of suitable ("best") ligands** for specific receptors in proteins.
- **Ligands** can act either as **activators** or as **inhibitors** of the biological function of the protein in the cell.
- **Artificial ligands** (i.e. drugs) can be used to up-regulate or down-regulate the activity of proteins that are associated with specific diseases.
- To the left, **HIV-1 Protease** complexed with an efficient **inhibitor**, TL-3-093.

Docking

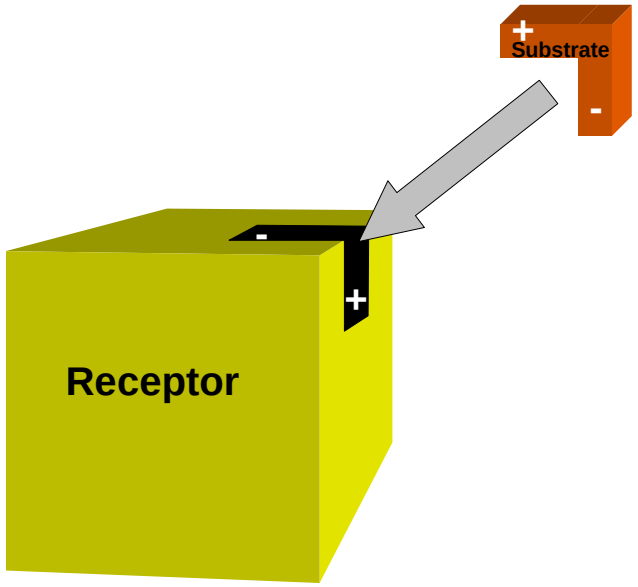
- Three-dimensional molecular structure is one of the foundations of **structure-based drug design**.

- Often, data are available for the shape of a **protein** and a **drug** separately, but not for the two together.

- **Docking** is the process by which two molecules fit together in 3D space.

Docking

- Two general classes
  - "Unbiased"
    - Autodock
  - "Direct"
    - DOCK
    - LUDI
- Goals
  - Robust and accurate
  - Computationally feasible



Ligand-Receptor Docking Approach: Challenges

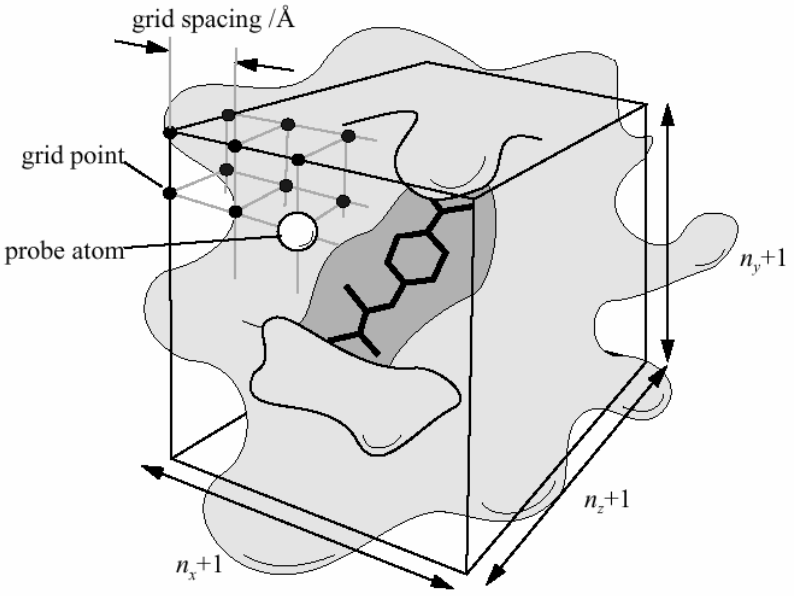
- Must screen **millions** of possible compounds that fit a particular receptor.
- Must **specifically select** those ligands that show a **high affinity**.
- The **set of ligands** selected can then be **screened further** by more involved computational techniques, such as free-energy perturbation theory (ΔG_{bind})
- We would like an **automated, standard protocol** to find the best Ligand-Receptor fit.

Docking

- Terms to consider in docking
  - Shape complementarity
  - Interaction specificity
  - Solvation/desolvation
  - Hydrophobic
  - Hydrogen bonding
- Terms considered in MOE-Dock (Autodock)
  - Van der Waals
  - Hydrogen bonding
  - electrostatics

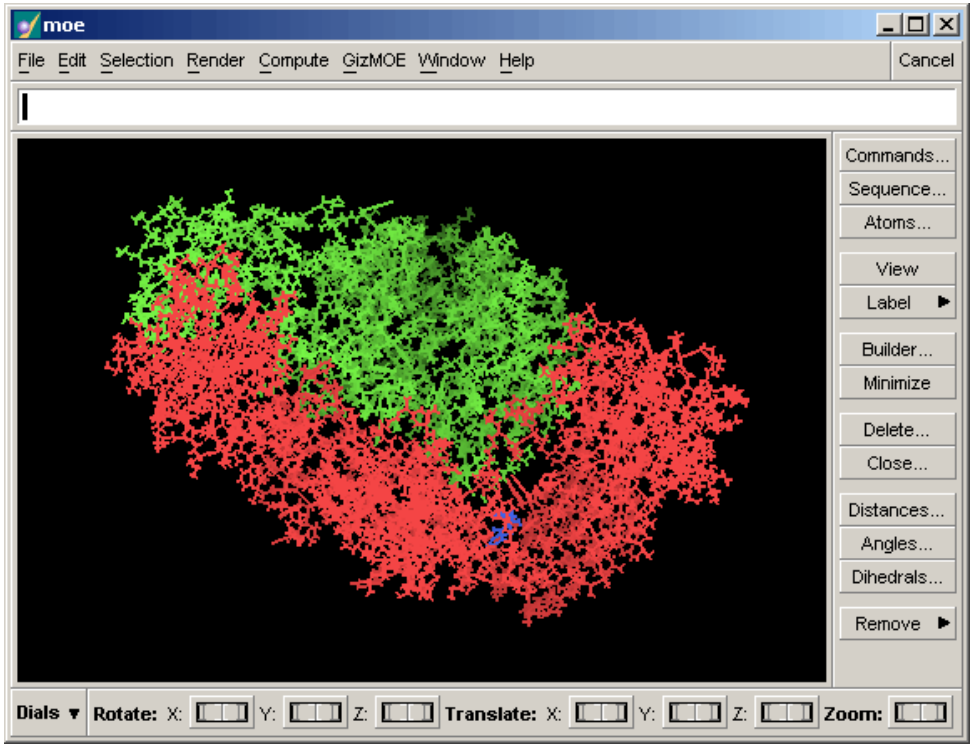
Docking

- Energy evaluation
  - Based on a Grid approach
- Search engine
  - Simulated Annealing (SA)
    - Autodock
    - MOE-Dock
  - Genetic Algorithms (GA)
    - Autodock 3.0



MOE-Dock Application

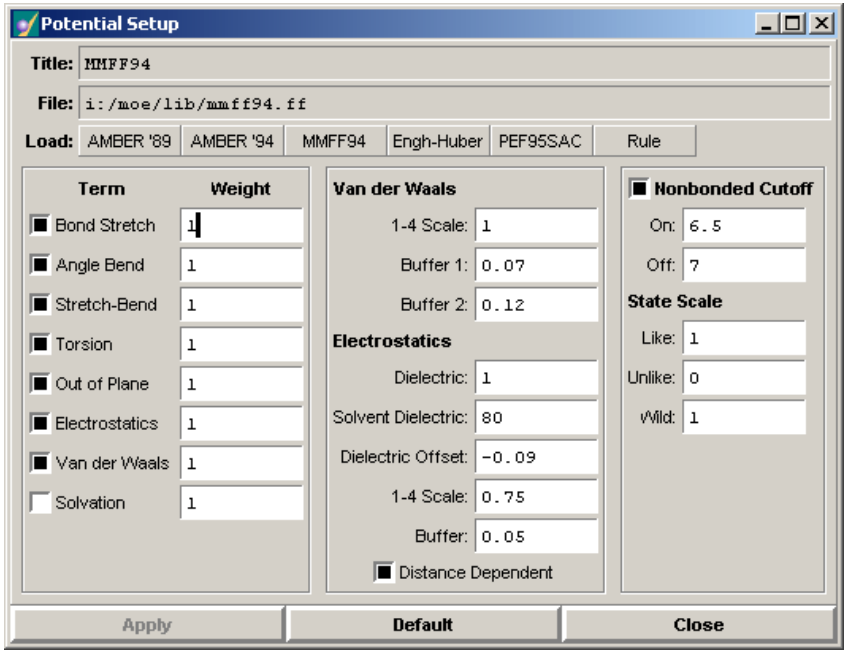
- We will look at a docking example of a TIBO-like inhibitor to HIV-1 Reverse Transcriptase (HIV-RT).
- Crystal structure to be used: HIV-RT with TIBO-R86183.



MOE-Dock Application

- Setting up the calculation.
  - *Prepare the protein*. Color the ligand, receptor, and metal ions distinctly. Add H atoms to the X-ray structure if none are given
    MOE | Edit | Add Hydrogens
  - *Select ForceField.*
    MOE | Window | Potential Control
  - *Minimize*.

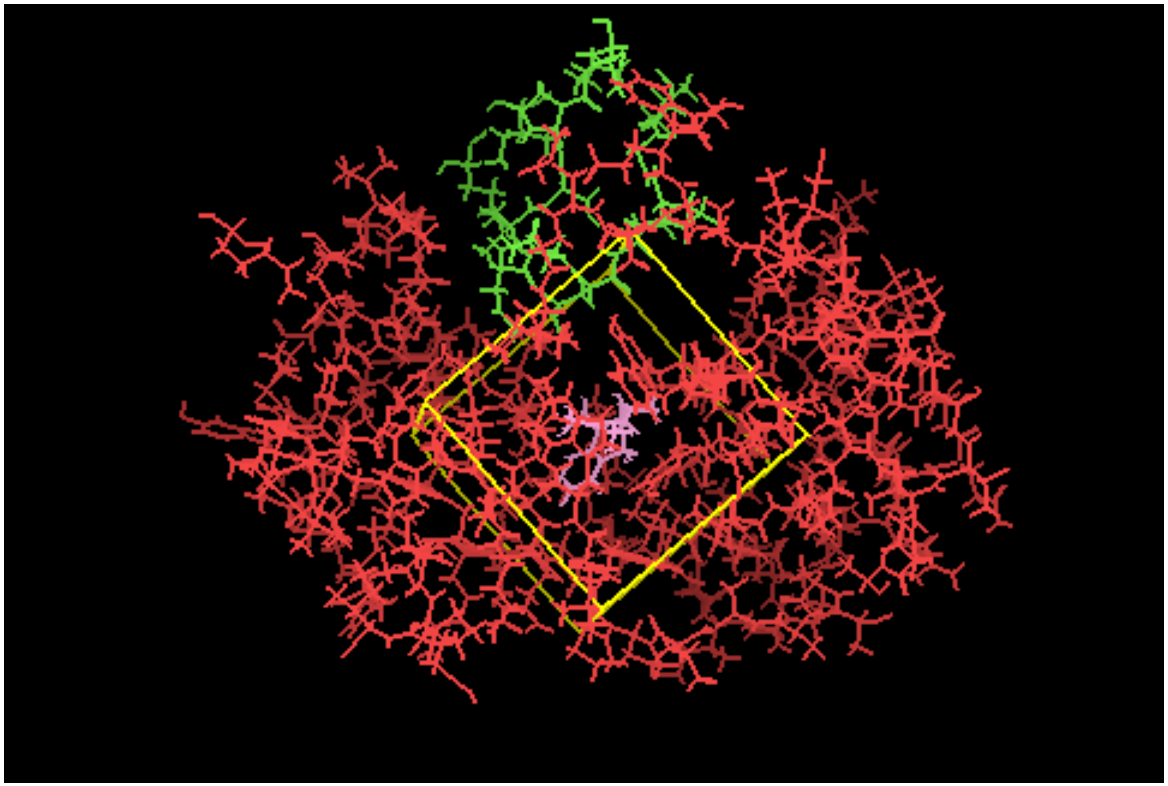
    MOE | Compute | Energy Min.



Here you can turn on solvation model;
Place partial charges on atoms

MOE-Dock Application

- MOE | Compute | Simulations | Dock

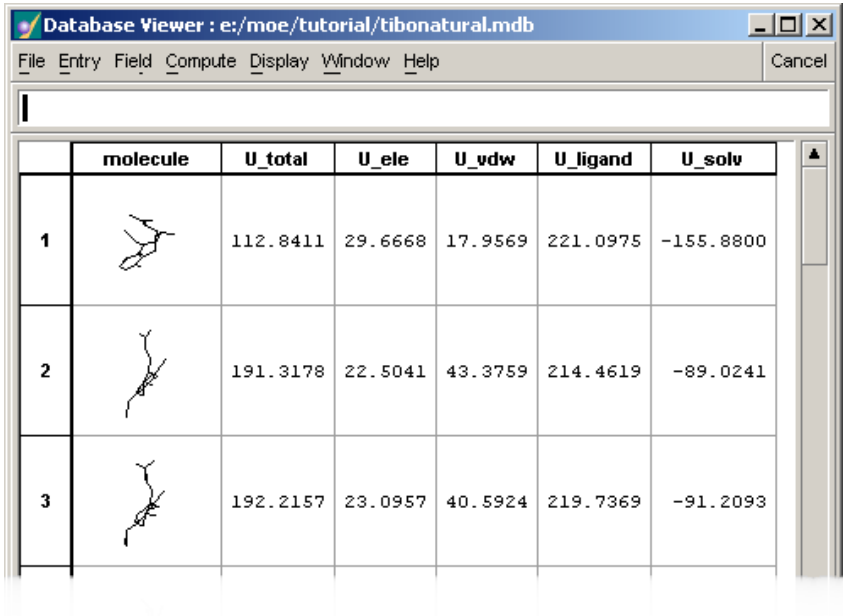


The docking box appears around the ligand.

Graphic shows HIV-RT (red) and its ligand TIBO-R86183.

MOE-Dock Application
Docking Results

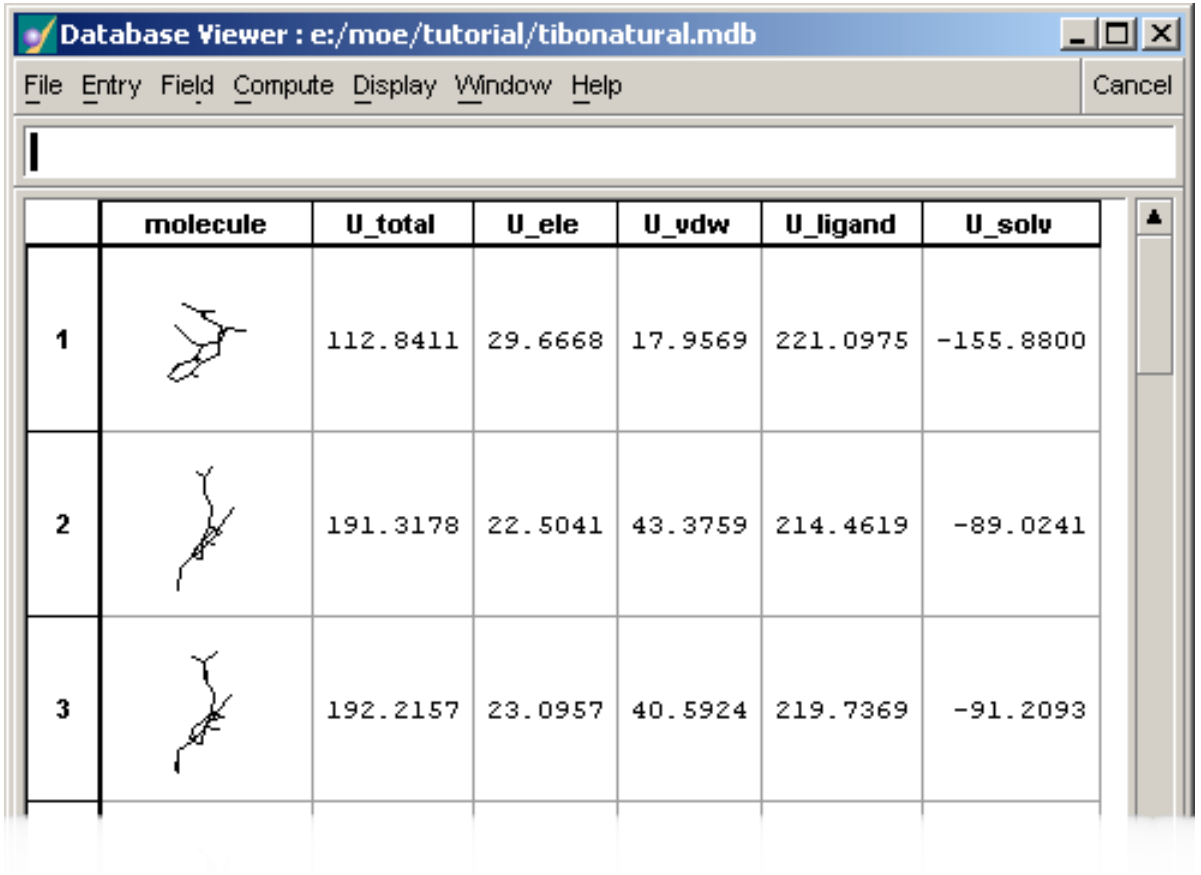
- Examine the docked structures compared to the crystal structure of the ligand and its receptor.
- In this database, columns contain the total energy of the complex, the electrostatic (U_ele) and van der Waals energies (U_vdw) between the protein and the ligand, and the energy of the (flexible) ligand (U_ligand).



	molecule	U_total	U_ele	U_vdw	U_ligand	U_solv
1		112.8411	29.6668	17.9569	221.0975	-155.8800
2		191.3178	22.5041	43.3759	214.4619	-89.0241
3		192.2157	23.0957	40.5924	219.7369	-91.2093

MOE-Dock Application

- **To find the best (lowest energy) docked structure**, you will sort the database in ascending order with respect to the total energy (U_total)

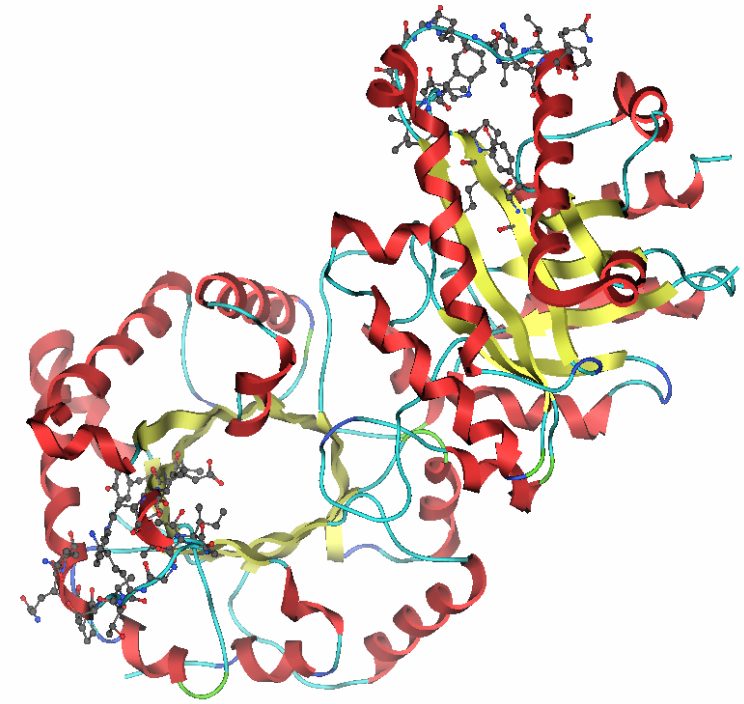


	molecule	U_total	U_ele	U_vdw	U_ligand	U_solv
1		112.8411	29.6668	17.9569	221.0975	-155.8800
2		191.3178	22.5041	43.3759	214.4619	-89.0241
3		192.2157	23.0957	40.5924	219.7369	-91.2093

Brownian Dynamics

Triose Phosphate Isomerase

- Enzyme that catalyzes the interconversion of D-glyceraldehyde phosphate (GAP) to dihydroxyacetone phosphate (DHAP)
- Rate-limiting step of TIM with GAP as substrate is diffusion-controlled (k_d = 4.8 x 10^8 M^{-1} s^{-1})



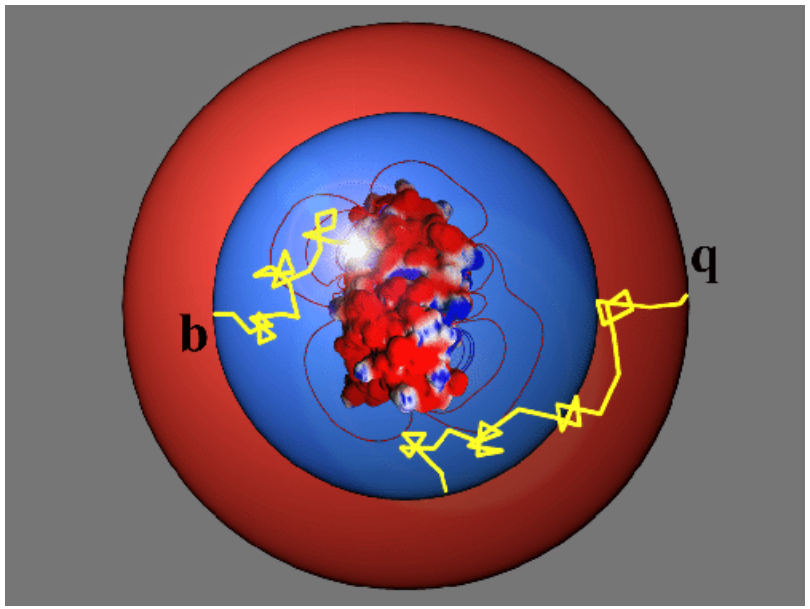
Substrate	**Calculated Rate Constant (10^8 M^{-1} s^{-1})**
Sphere	148.
Sphere (no electrostatics)	30.6
Dumbbell	1.664
Flexible loop / dumbell	4.2

Bimolecular Diffusion-Controlled Rate Constant

Diffusion constant

$$\vec{r}' = \vec{r}_0 + \frac{D\vec{F}(\vec{r}_0)}{k_B T}\Delta t + \vec{R}$$

Random vector



$$\beta = \frac{\#\ of\ \ hits}{\#\ of\ \ trials}$$

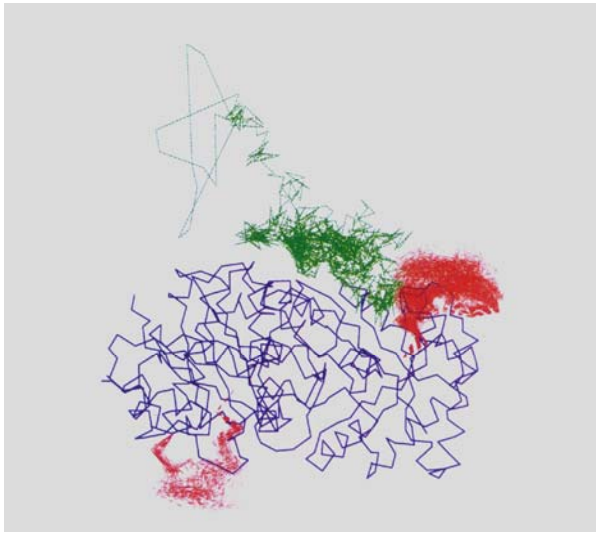
$$k = k_D(b)[1 - (1 - \beta)\Omega]^{-1}$$

$$k_D(b) = 4\pi \frac{\int_b^\infty dr\, e^{(U(r)/k_B T)^{-1}}}{4\pi r^2 D(r)}$$

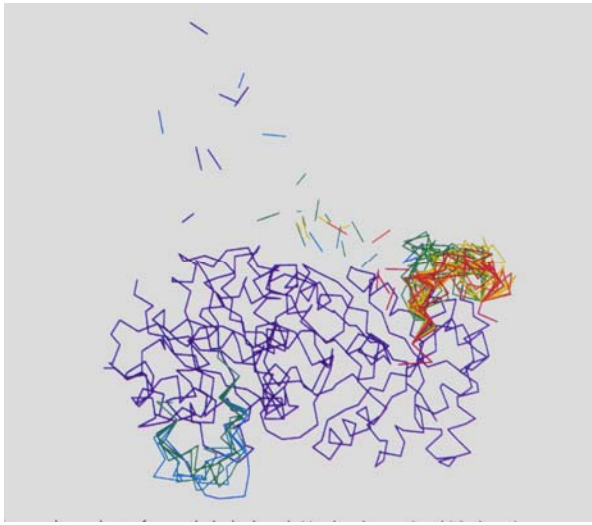
$$\Omega = \frac{k_D(b)}{k_D(q)}$$

Diffusional Encounter between GAP and TIM

- Snapshot of a ~11 ns trajectory of GAP diffusing to the active site of TIM. In the top figure the random nature of the substrate (shown in green) and the large volume of space sampled can be seen.

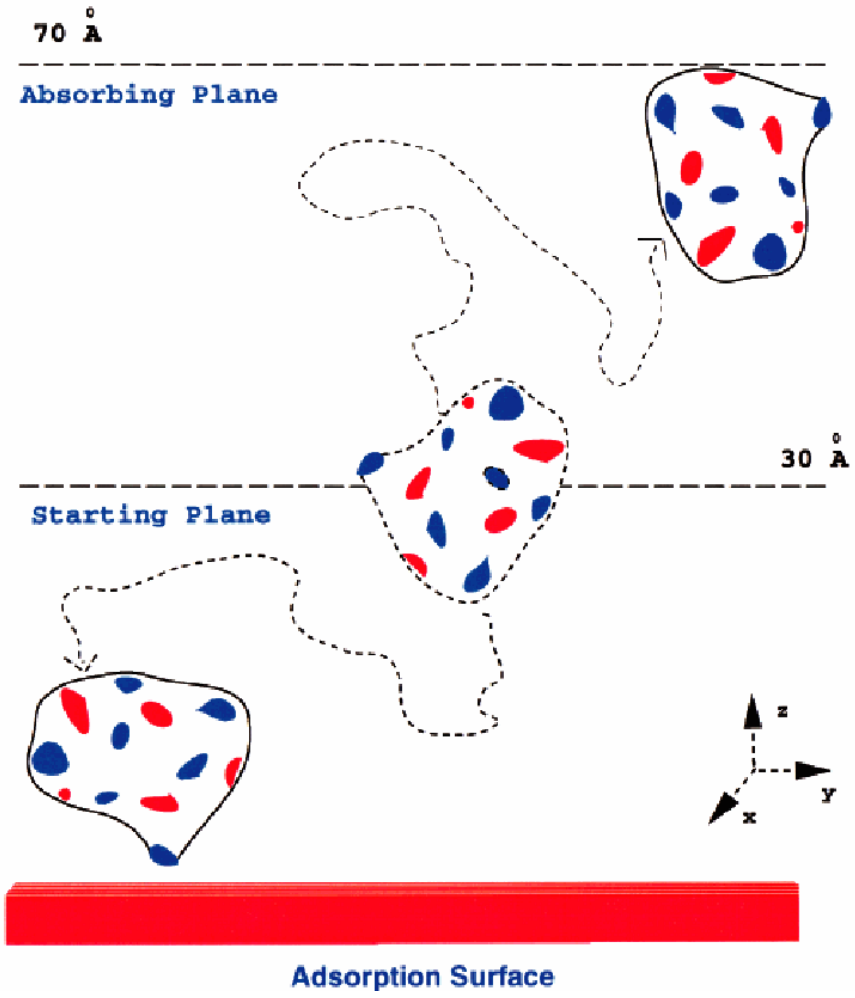


- The bottom figure illustrated 32 snapshots at intervals of 0.25 – 1 ns colored according to time (indigo to red corresponds to increasing time)

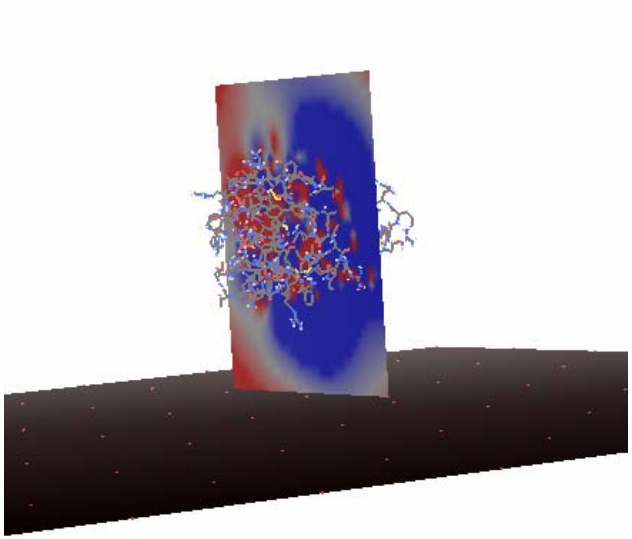


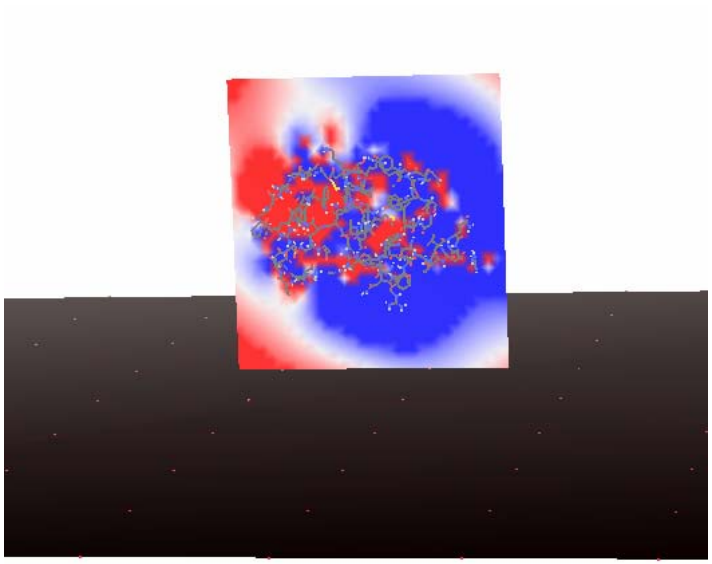
Brownian Dynamics Simulation of Lysozyme to a Charged Surface

- Schematic diagram showing the details of the simulation method. In this figure the protein molecule is represented as an arbitrarily shaped object with patches corresponding to both positively charged (blue) and negatively charged (red) amino acid residue collections.



Protein – Surface Interactions





Fraction of Successful Trajectories for Two Different Salt Concentrations

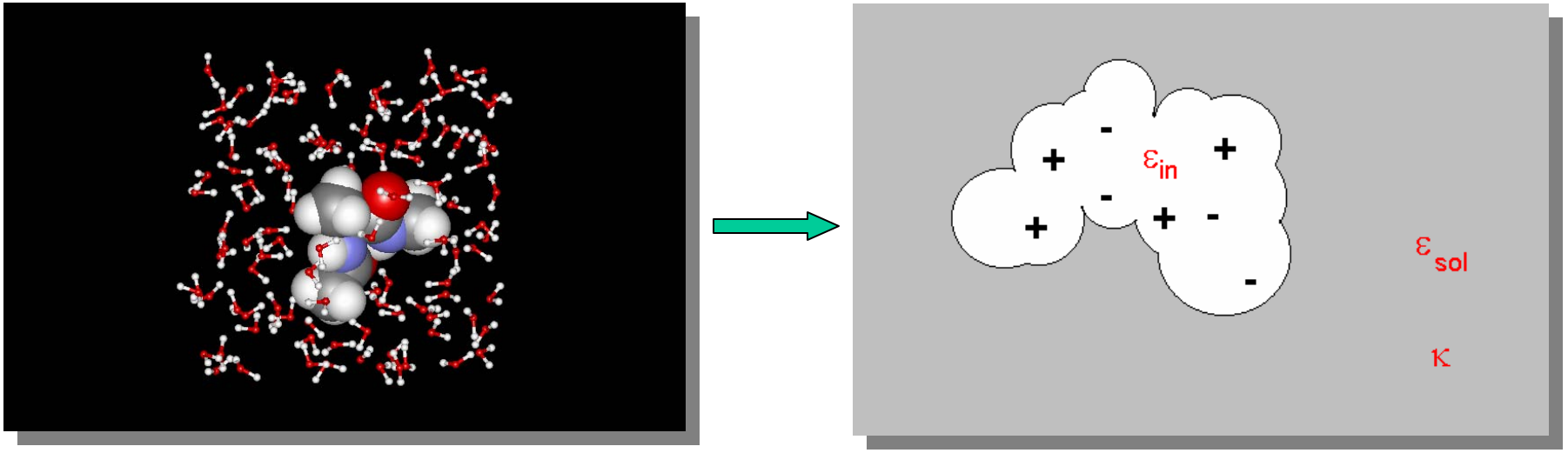
I(M)	Successful Trajectories
0.1	0.71 ± 0.03
0.3	0.64 ± 0.02
No Electrostatics	0.62 ± 0.03

Poisson – Boltzmann Electrostatics

Application Areas of Electrostatics

- Electrostatic Energies
- Electrostatic Forces
- Electrostatic Binding Free Energy
- Electrostatic Solvation Free Energy
- pKa Shifts
- Protein Stability
- Conformational pH Dependence
- Redox
- Electrostatic Steering in Enzyme/Substrate Encounters
- Electrostatic Forces Coupled to Molecular Mechanics/Dynamics

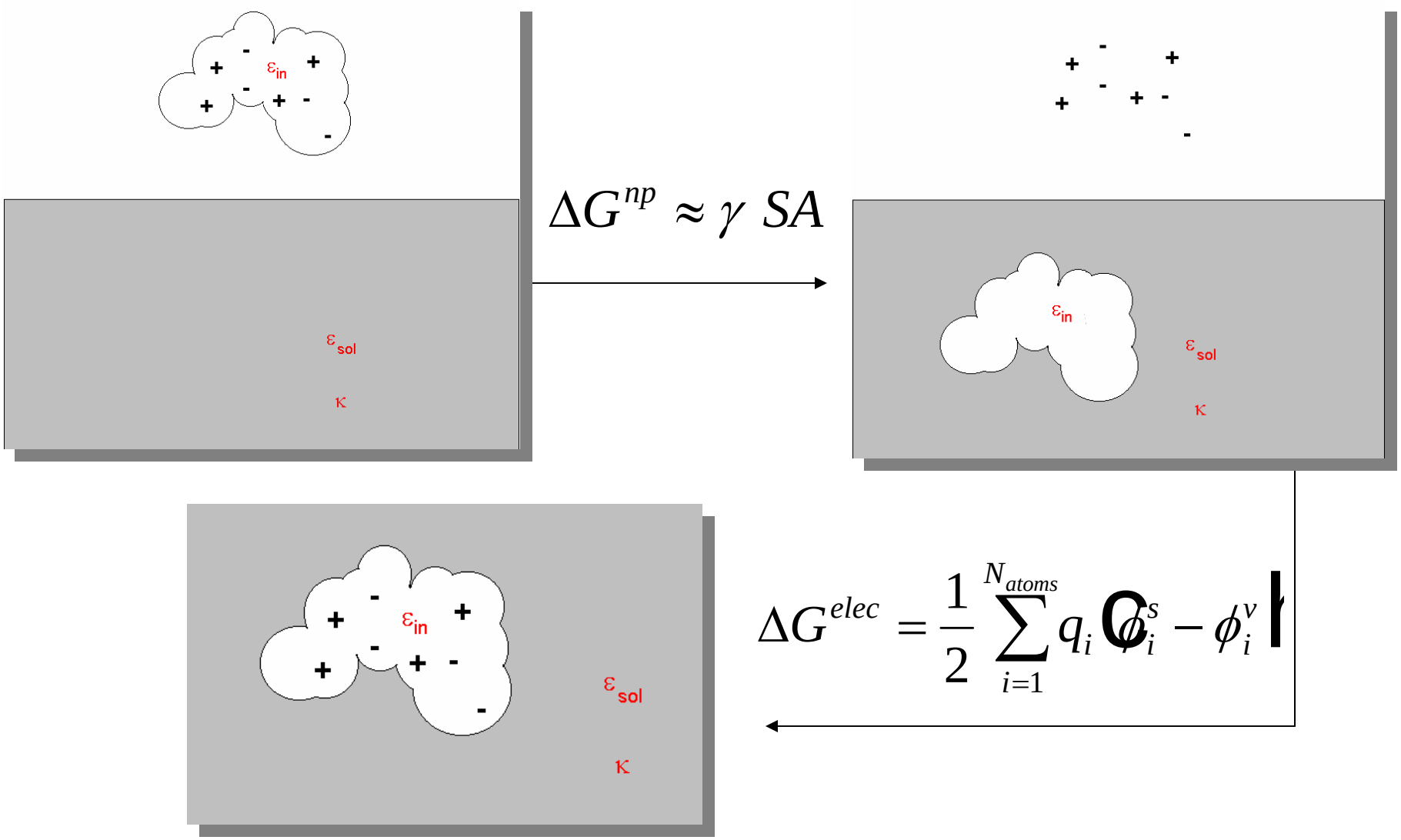
Explicit vs. Continuum Solvent Model



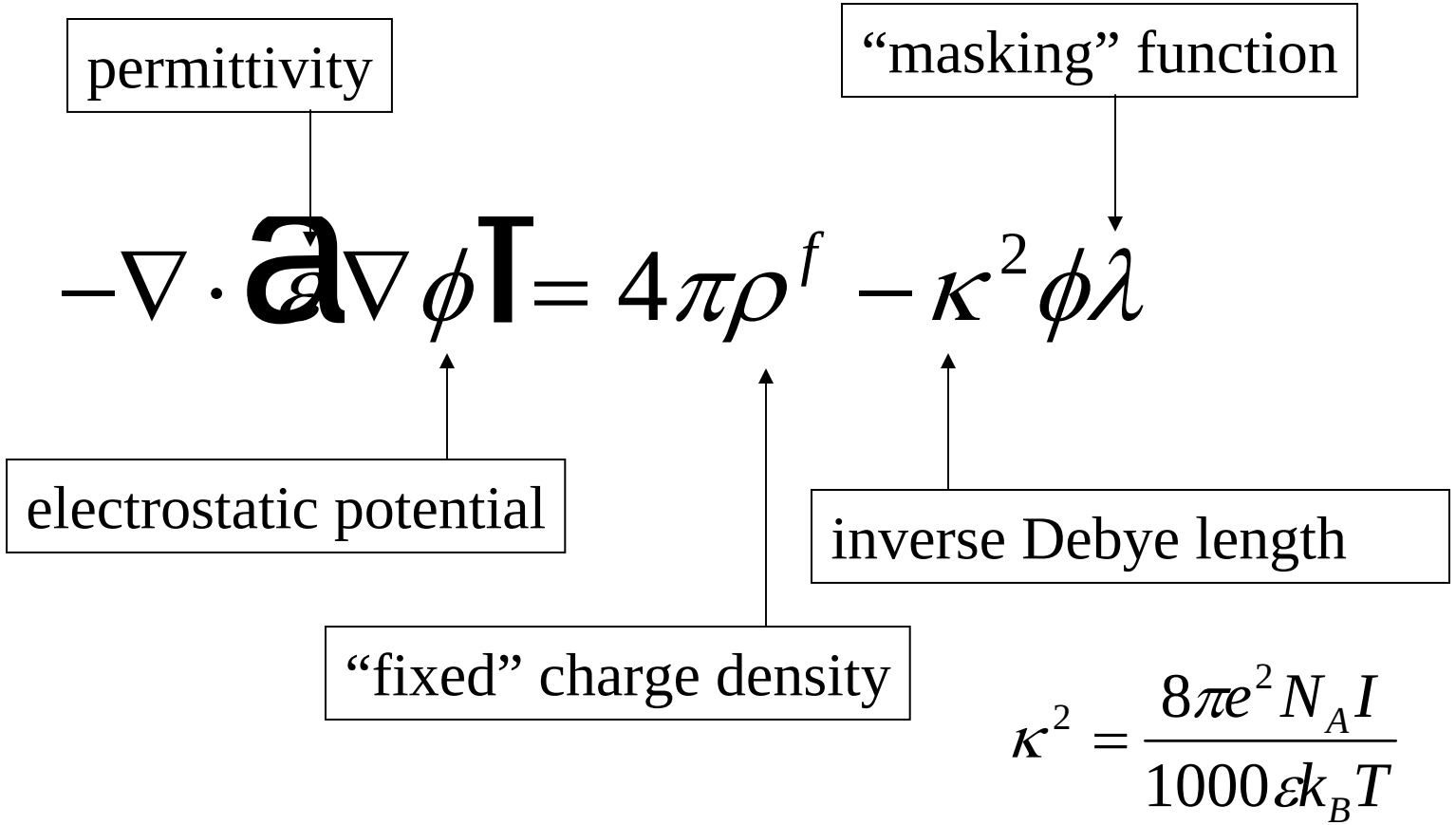
Based on a suggestion by Born, the explicit solvent model may be very crudely approximated by a structureless continuum. In this continuum picture the solvent is represented by a dielectric constant, ε_{sol}, and the effect of ions by, κ. The solute is a set of embedded charges inside a cavity with a dielectric constant of, ε_{in}.

Continuum Solvent Model

$$\Delta G^{solv} = \Delta G^{np} + \Delta G^{elec}$$



Poisson-Boltzmann Model of Molecular Electrostatics



$$\kappa^2 = \frac{8\pi e^2 N_A I}{1000 \varepsilon k_B T}$$

Solving the FDPB Equation

- In practice, one knows the
  - charge density (ρ) from the fixed charges in the receptor and substrate.
  - the permittivity (dielectric constant).
  - Kappa (κ), which is related to the ionic strength.
- Make a guess at the potential.
- Solve the equation for a new potential.
- Continue to solve until the change in potential is small.

Poisson-Boltzmann Electrostatic Forces

$$\vec{f} = F^{Coul} + F^{RF} + F^{DBF} + F^{IBF}$$

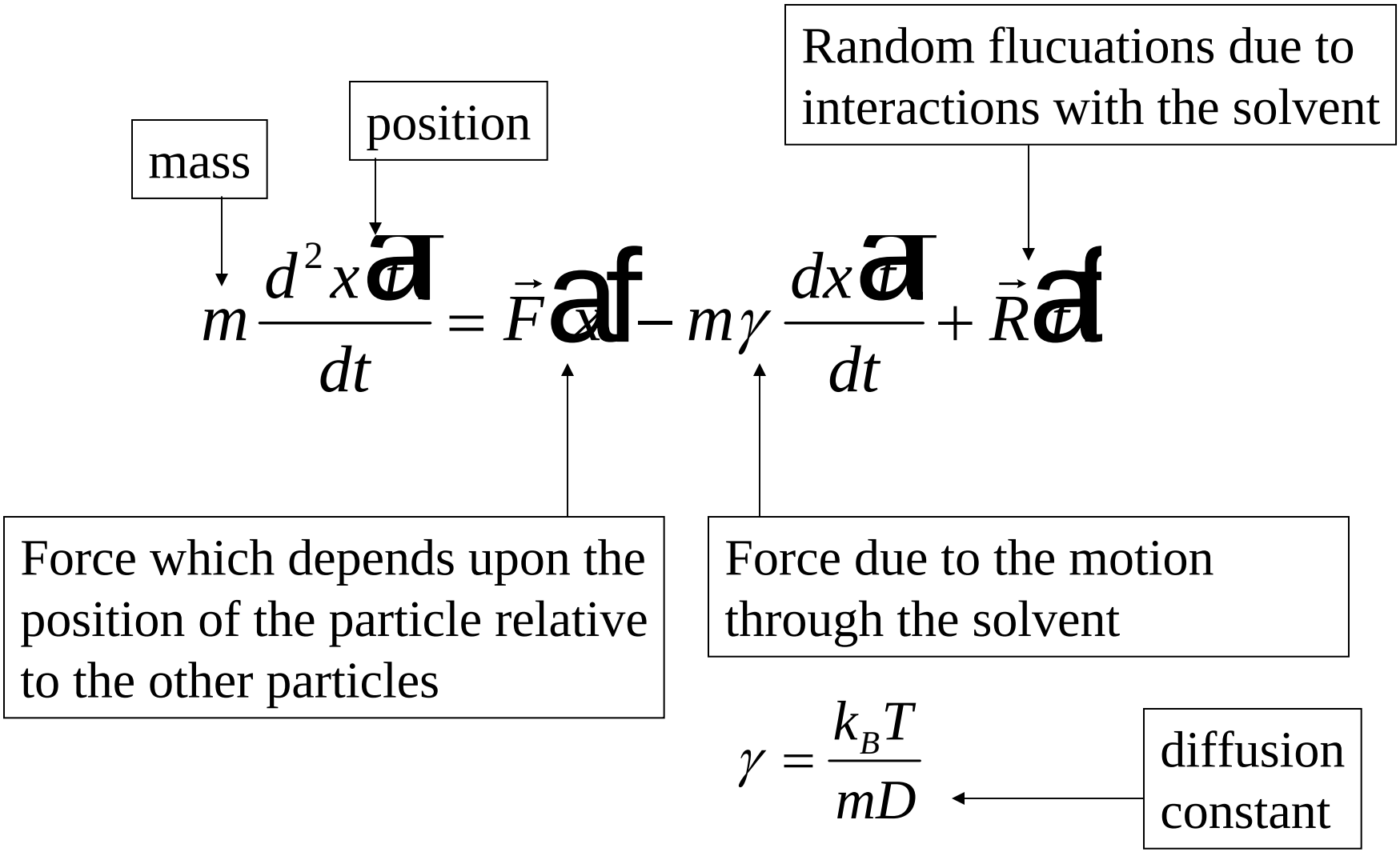
$\boldsymbol{F^{Coul}}$ is the Coulombic force which is the interaction of all the solute atoms with each other and is referred to as the "qE" force.

$\boldsymbol{F^{RF}}$ is the reaction field force, $F^{RF} = qE^{RF}$ where E^{RF} is the solvent reaction field acting at an atom.

$\boldsymbol{F^{DBF}}$ is the dielectric boundary force. This is due to the tendency of high dielectric medium to reduce the field energy by moving into regions of low-dielectric constant.

$\boldsymbol{F^{IBF}}$ is the ionic boundary force and is generally small in comparison with the other forces in the system. This force results from the tendency of mobile ions to reduce the field energy by moving into regions of zero ionic strength (i. e. the molecular interior).

Langevin Dynamics

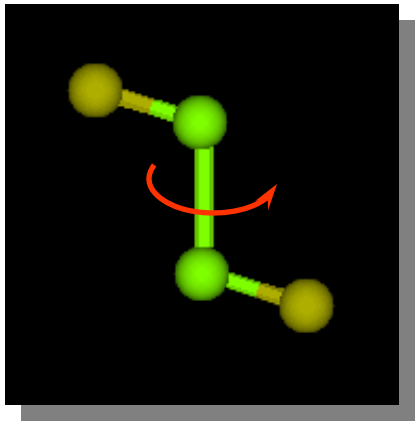


Dichloroethane

Summary of simulation parameters

$\varepsilon_i = 1$
$\varepsilon_s = 80$
$\gamma = 6.5\ ps^{-1}$
dt = 0.001 ps
T = 1000 K
grid spacing = 0.5 to 1.2 A

Atom Type	Charge (e)	Radius (Å)
Cl	-0.25	1.82
CH_2	0.25	1.99

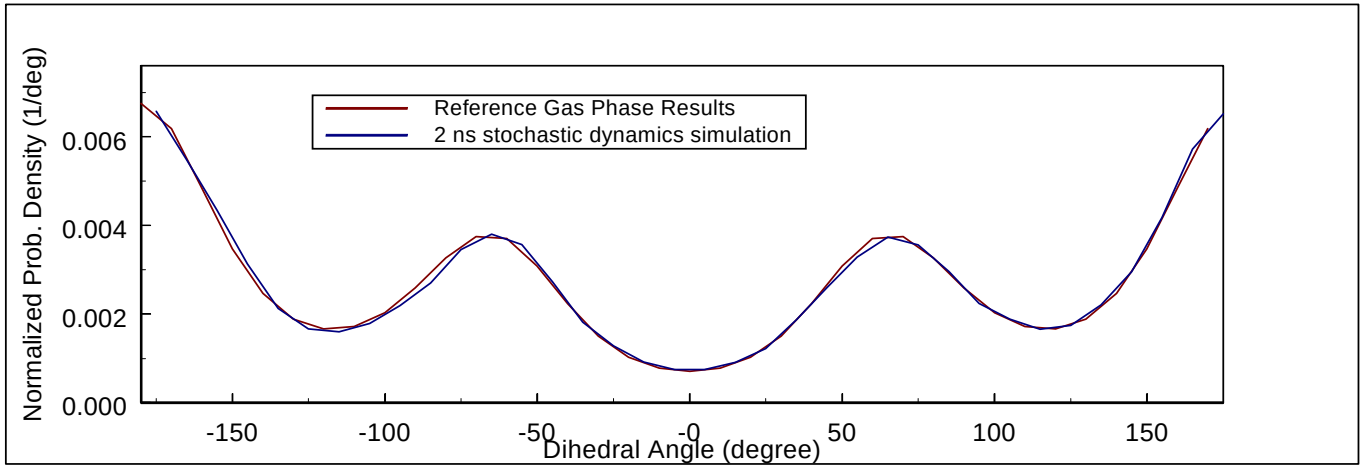


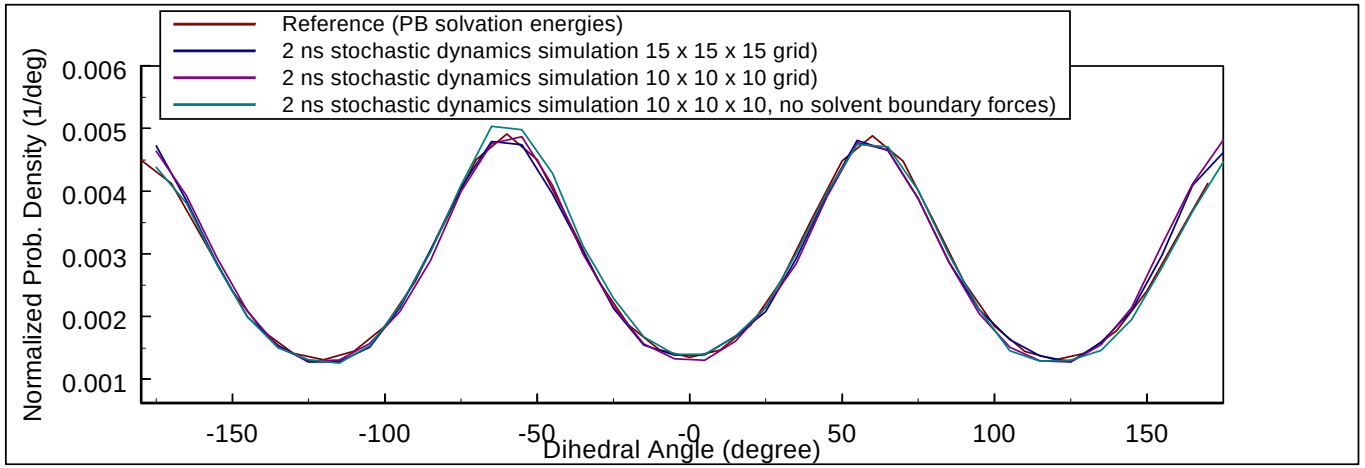
Trans conformer dominates in the gas phase

Increased gauche conformer in liquid phase

Dichloroethane

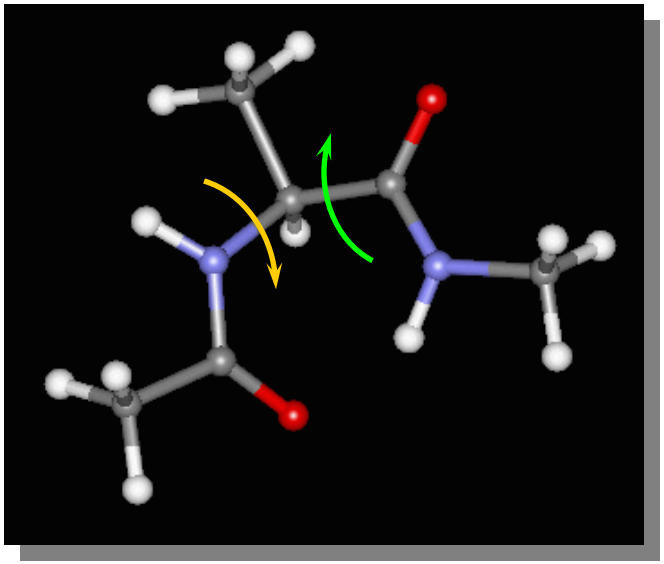
Summary of simulation results





Alanine “dipeptide”

Summary of simulation parameters



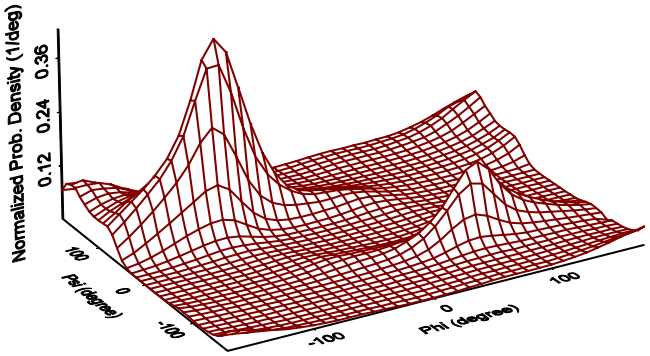
$\varepsilon_i = 1$
$\varepsilon_s = 80$
$\gamma = 6.5\ ps^{-1}$
dt = 0.001 ps
T = 1000 K
grid spacing = 0.7 to 1.7 A

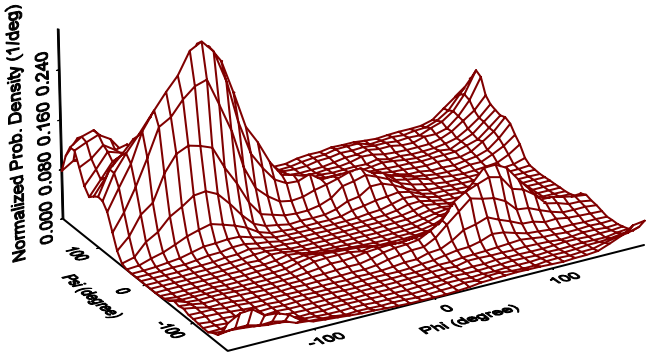
Conclusions

Good equilibration
Good agreement with other computational models
Weak sensititvity to grid spacing
No heating from numerical forces

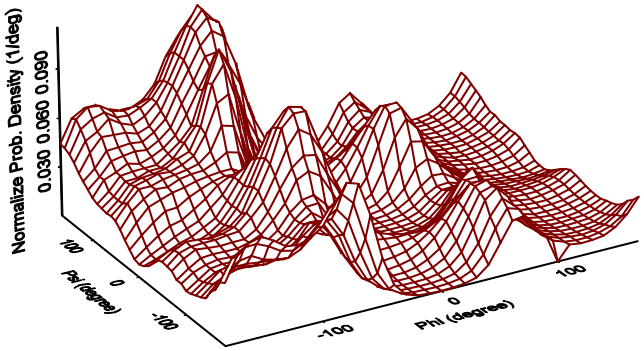
Alanine “dipeptide”

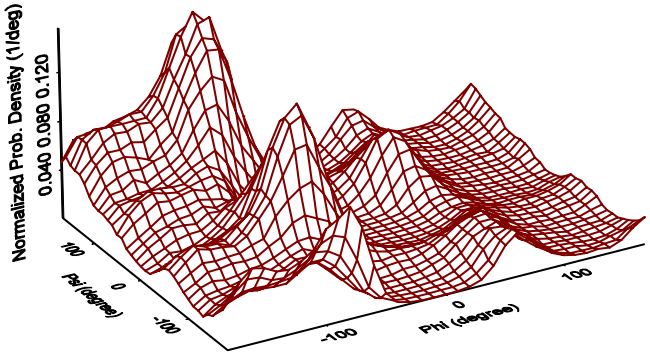
in vacuo





Aqueous



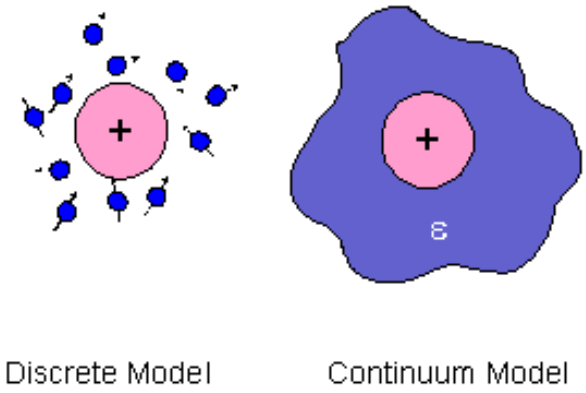


Reference

2 ns stochastic dynamics

Thermodynamic Treatment of Ion-Solvent Interactions: *The Born Model*

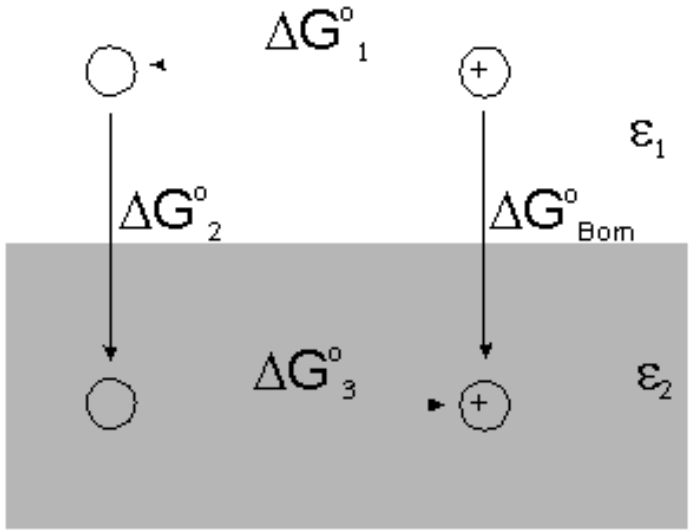
- **Ion-Solvent interaction**: Consists of solvent dipoles interacting with the electric field of the ion.
- **Two cases to consider for the solvent**:
  - A structure-less **continuum** of dielectric ε ("The Born Model")
  - **Discrete molecules** with dipoles, polarizability, etc.



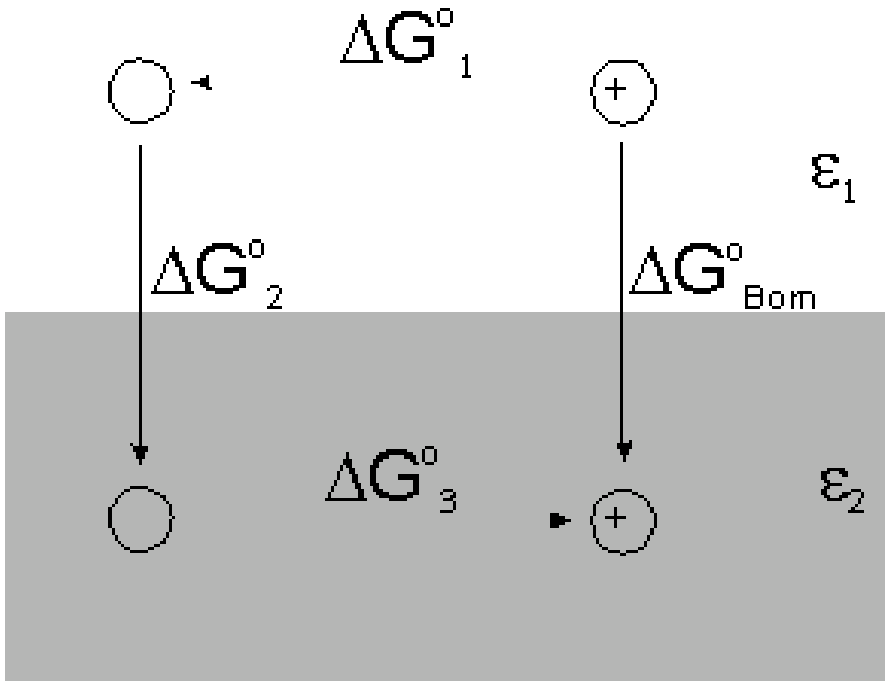
The Born Model

- Consider: Continuum model of ion solvation.

If medium 1 is a vacuum, ΔG_{born}. is just the free energy of solvation.



We will calculate the free energy of **transfer of an ion from medium 1 (ε_1) to medium 2 (ε_2).** This will be called ΔG_{born}.



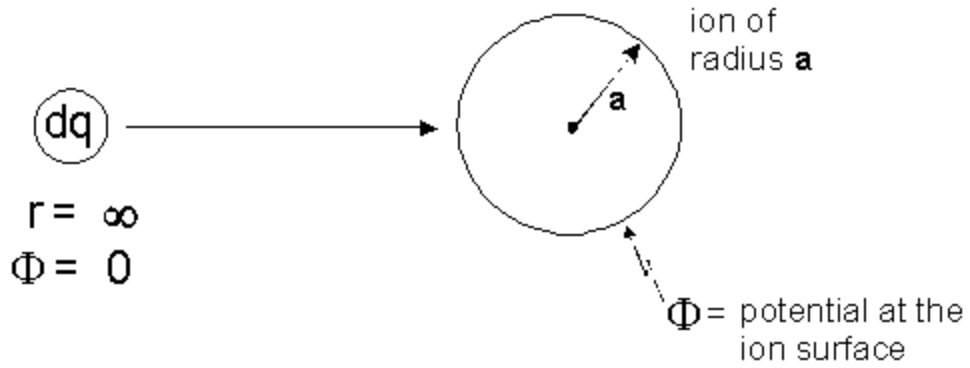
$$\Delta G_{Born} = \Delta G_1^o + \Delta G_2^o + \Delta G_3^o$$

The path for ΔG_{born} refers to:

First **discharging** the ion in medium 1 (ΔG^o_1)
Transferring the ion from medium 1 to medium 2 (G^o_2)
Recharging the ion in solvent 2 (ΔG^o_3)

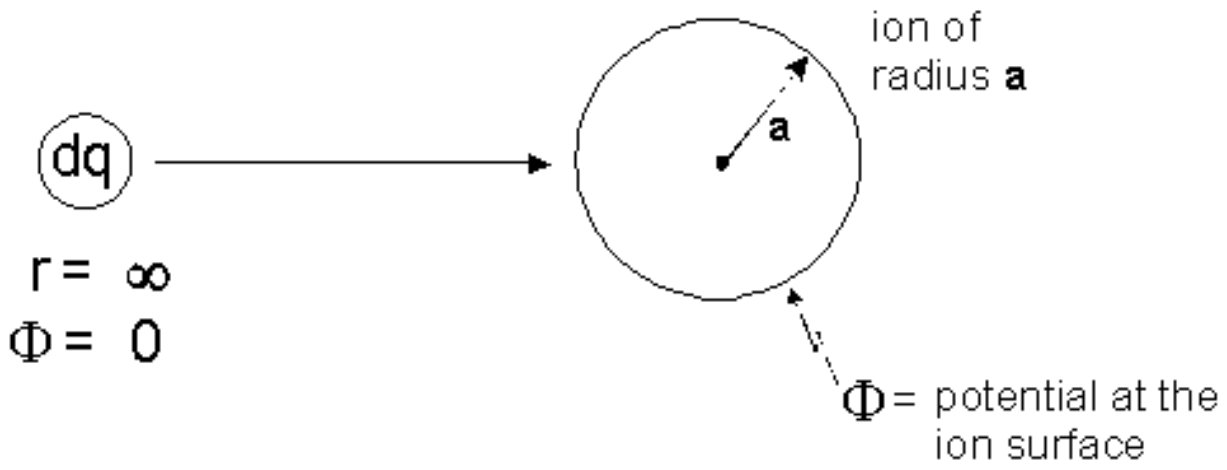
The Charging Process

- Energies of charging/discharging:
  - computed by a model where *infinitesimal pieces of charge* are brought from infinity,
  - and placed on the surface of the ion until the final charge is obtained



The charging process

The Charging Process



The charging process

What is the energy of bringing a charge dq from infinity and placing it on the surface of a sphere with radius a?

$$dG = \Phi dq$$

The Charging Process

- Knowing the potential (Φ) of a point charge, we have,

$$dG_{charging} = \Phi dq = \frac{q}{4\pi \varepsilon_o \varepsilon a} dq$$

Integrating this from 0 to the final charge on the ion, Ze (where Z is the valence)…..(Next Slide)

The Charging Process

$$\Delta G_{charging} = \frac{Z^2 e^2}{8\pi \varepsilon_o r}$$

Therefore, For ΔG^o_1 , ΔG^o_2, and ΔG^o_{born} we have…(Next Slide)

$$\Delta G_{discharging} = -\Delta G_{charging}$$

The Charging Process

$$\Delta G_1^o = -\frac{Z^2 e^2}{8\pi \varepsilon_o \varepsilon_1 a}$$

$$\Delta G_2^o = +\frac{Z^2 e^2}{8\pi \varepsilon_o \varepsilon_2 a}$$

$$\Delta G_{Born}^o = \frac{Z^2 e^2}{8\pi \varepsilon_o a}\left(\frac{1}{\varepsilon_2} - \frac{1}{\varepsilon_1}\right) + \Delta G_2^o$$

If $\varepsilon_2 < \varepsilon_1$, then $\Delta G^o > 0$

It takes work to move an ion from water to a less polar solvent (such as vacuum or hydrocarbon)

Free Energy of Solvation

- Consider: Transferring an ion from a vacuum to a medium of ε.
  - Assume $\Delta G^{o}_{2} = 0$. (No interaction between solvent and discharged ion).

$$\Delta G^{o}_{solvation} = \frac{Z^2 e^2}{8\pi \varepsilon_o a}\left(\frac{1}{\varepsilon} - 1\right)$$

Two points to note:

1. $\Delta G < 0$ if $\varepsilon > 1$
2. ΔG increases as ionic Radius increases. Why? The field and the potential At the ion surface becomes Less.

Generalized Born

- Widely used to represent the electrostatic contribution to the free energy of solvation
- Model is comprised of a system of particles with radii a_i and charges q_i
- The total electrostatic free energy is given by the sum of the Coulomb energy and the Born free energy of solvation in a medium of relative permittivity ε.

$$G_{elec} = \sum_{i=1}^{N} \sum_{j=i+1}^{N} \frac{q_i q_j}{\varepsilon r_{ij}} - \frac{1}{2}\left(1 - \frac{1}{\varepsilon}\right) \sum_{i=1}^{N} \frac{q_i^2}{a_i}$$

Generalized Born

- The previous equation can be re-written into the generalized Born equation

$$\Delta G_{elec} = -\frac{1}{2}\left(1-\frac{1}{\varepsilon}\right)\sum_{i=1}^{N}\sum_{j=1}^{N}\frac{q_i q_j}{f\left(r_{ij}, a_{ij}\right)}$$

- $f(r_{ij},a_{ij})$ depends upon the interparticle distances r_{ij} and the Born radii a_i.

$$f\left(r_{ij}, a_{ij}\right) = \sqrt{r_{ij}^2 + a_{ij}^2 e^{-D}}$$

$$a_{ij} = \sqrt{a_i a_j} \qquad D = \frac{r_{ij}^2}{\left(2a_{ij}\right)^2}$$

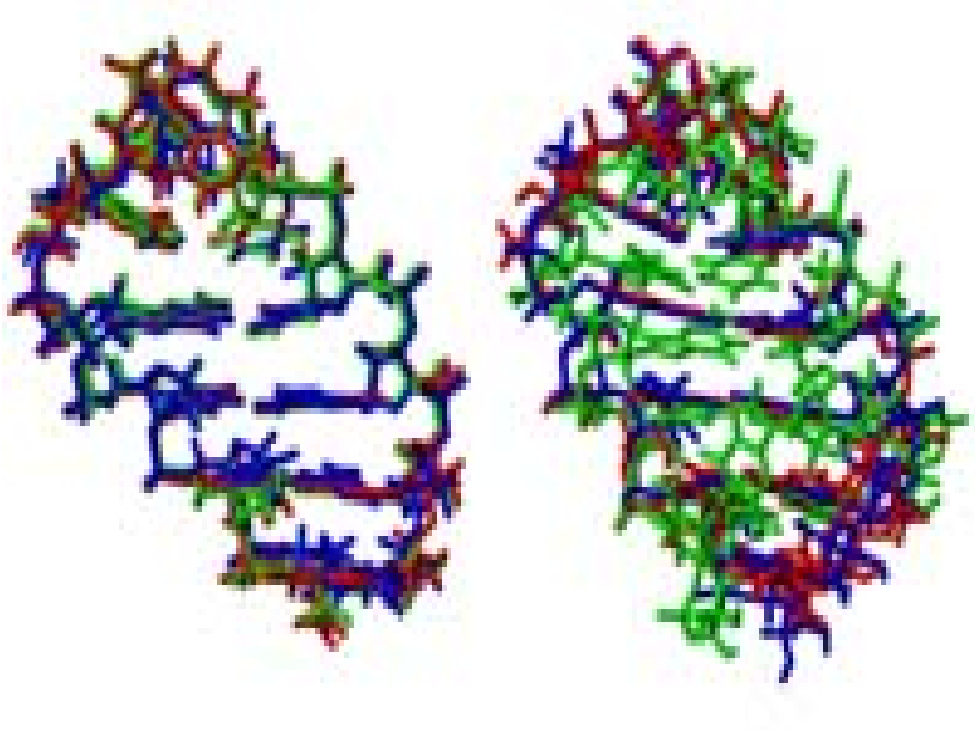
Generalized Born

- Note the following
  - When $i=j$ the equation returns the Born expression
  - When $r_{ij} << a_i$ and a_j the expression is close to the Onsager result (I.e. a dipole)
  - When $r_{ij} >> a_i$ and a_j the result is very close to the sum of the Coulomb and Born expression
- A major advantage to this formulation is that the expression can be differentiate analytically, thereby enabling the solvation term to be included in gradient-based optimization methods

MacroModel GB/SA Solvation Model

- Accounts for solvation effects, especially in complex systems.
- Generalized Born/Surface Area (GB/SA) approach (continuum).
  - increases the speed of the calculation
  - avoids convergence problems, apparent in explicit models, where longer simulations or different solvent starting geometries yield different final energies.
- The GB/SA model can be used to calculate absolute free energies of solvation.

Application of GB/SA Solvation Model

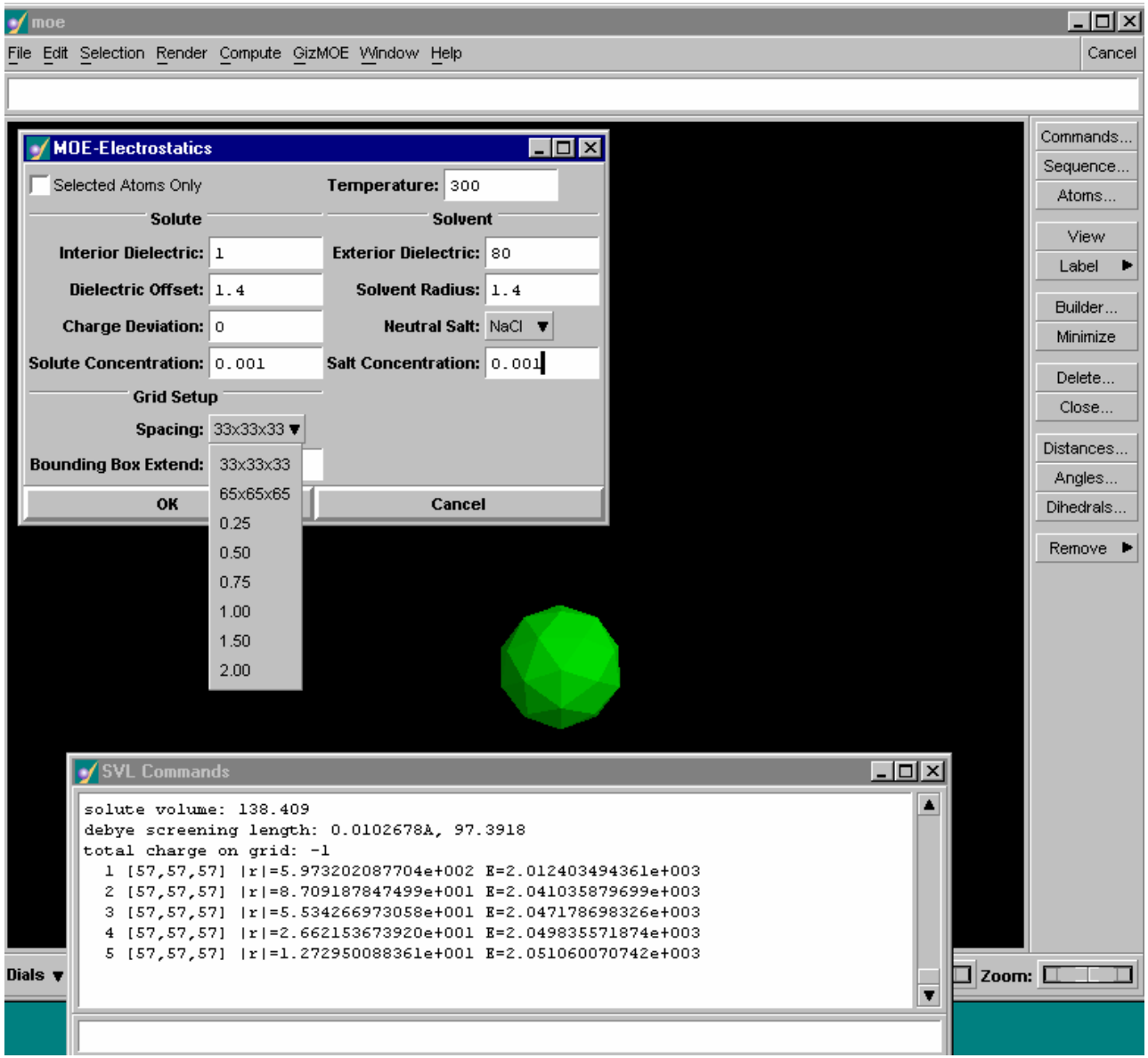


- Hall group applied the GB/SA continuum solvation model to RNA hairpins with much success.
- Simulations of the UUCG tetraloop give average structures within 1.2 Å of the initial NMR model, in agreement with an explicit solvent simulation (Williams, D. J., Hall, K. B. 1999. Biophys J. 76:3192-3205).

Electrostatic Free Energy of Solvation Calculation

- In this calculation one computes the electrostatic energy difference between the molecule in the aqueous phase and in vacuum.
  - This is equivalent to computing the work in moving a charge from a low dielectric to a high dielectric.
  - This work is equivalent to a change in the free energy.
  - MOE-Electrostatics can be used by performing two calculations
    - Compute the electrostatic energy with both dielectric constants set to 1
    - Compute the electrostatic energy with the interior dielectric set to 1 and the exterior dielectric set to 80.

MOE-Electrostatics



For the chloride ion we have

EE: 1/80 = 2472.76

EE: 1/1 = 2545.44

$\Delta EE = \Delta G = -72.68$

From the Born equation we have

$$\Delta G = -332 \frac{q^2}{2a}\left(1 - \frac{1}{\varepsilon}\right)$$

ΔG = -67.79 kcal/mol

Binding Free Energy

- Consider the following noncovalent binding process

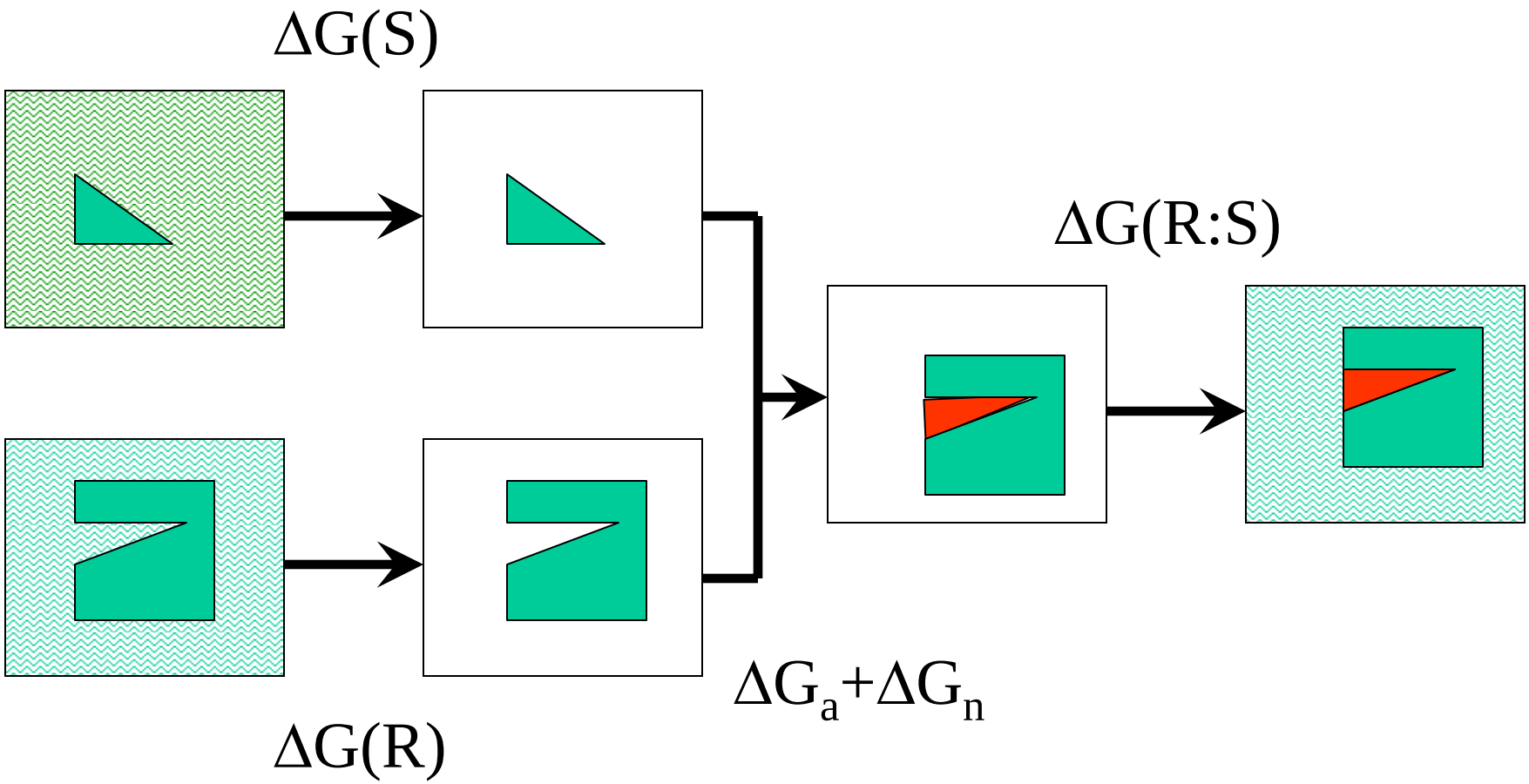
$$R + S \Leftrightarrow R:S$$

- Where R represents to receptor, S represents the substrate and R:S is the noncovalent complex.
- The binding free energy can be partitioned into

$$\Delta G = \Delta G_s\left(R:S\right) - \Delta G_s\left(R\right) - \Delta G_s\left(S\right) + \Delta G_a + \Delta G_n$$

Binding Free Energy

- Pictorially the previous equation is



Binding Free Energy

- Relative binding free energies are best to compute ($\Delta\Delta G$)
- Results for sulphate-binding protein

Protein	$\Delta\Delta G_s$	$\Delta\Delta G_a$	$\Delta\Delta G_{calc}$	$\Delta\Delta G_{expt}$
S130G	-4.0	5.3	1.3	1.6
S130A	-2.4	5.3	2.9	2.7
S130C	-0.5	4.2	3.8	4.8

UHBD Capabilities

- The UHBD, University of Houston Brownian Dynamics, program is capable of computing a variety of properties for biomolecules
  - electrostatic binding free energy for an enzyme/substrate complex
  - bimolecular diffusion-controlled rate constant for an enzyme-substrate encounter with a flexible substrate
  - protein-protein association constants
  - perform a molecular mechanics / dynamics calculations using a continuum solvent
  - determining the pKa's of ionizable groups in proteins and small molecules.