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 inflammatory disease) caused by presence of \textit{in vivo} crystals of calcium pyrophosphate dihydrate (CPPD).
- Molecular aspect of \textit{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
MD Review

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

\[ \vec{F} = m \ddot{\vec{x}} = m \frac{d^2 \vec{x}}{dt^2} \]

- 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*
- *Direct comments to Alexander D. MacKerell Jr.*
- *410-706-7442 or email: alex@mmiris.ah.umd.edu*

27

! references

! PROTEINS

! 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

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 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 ! / | | \ ! 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 <<<<<<<<<<<
*>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
*>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
*>>>>>>>>> Direct comments to Alexander D. MacKerell Jr. <<<<<<<<<<<
*>>>>> 410-706-7442 or email: alex,nmirs.ab.umd.edu <<<<<<<<<<<
*
!PROTEINS
!
!C.; Michnick, S.; Ngo, T.; Nguyen, D.T.; Prodhom, B.; Reiner, 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
!
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)

\[ V(\text{angle}) = K_{\theta}(\theta - \theta_0)^2 \]
\[ V(\text{Urey-Bradley}) = K_{ub}(S - S_0)^2 \]

\begin{itemize}
  \item \( K_{\theta}: \text{kcal/mole/rad}^2 \)
  \item \( \theta_0: \text{degrees} \)
  \item \( K_{ub}: \text{kcal/mole/A}^2 \) (Urey-Bradley)
  \item \( S_0: \text{A} \)
\end{itemize}

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<th>( \theta_0 )</th>
<th>( K_{ub} )</th>
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\(^{\text{j}}\) atom types: \( K_{\theta} \theta_0 \) \( K_{ub} \) \( S_0 \) !

\(^{\text{JES}}8/25/89^{\text{J}} \)

\(^{\text{for 2-butene, yin/adm jr., 12/95}}^{\text{J}} \)

\(^{\text{for 1-butene; from propene, yin/adm jr., 12/95}}^{\text{J}} \)

\(^{\text{for 1-butene; from propene, yin/adm jr., 12/95}}^{\text{J}} \)

\(^{\text{for propene, yin/adm jr., 12/95}}^{\text{J}} \)

\(^{\text{6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93}}^{\text{J}} \)

\(^{\text{6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93}}^{\text{J}} \)

\(^{\text{6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93}}^{\text{J}} \)

\(^{\text{6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93}}^{\text{J}} \)

\(^{\text{6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93}}^{\text{J}} \)

\(^{\text{6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93}}^{\text{J}} \)

\(^{\text{6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93}}^{\text{J}} \)

\(^{\text{6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93}}^{\text{J}} \)

\(^{\text{6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93}}^{\text{J}} \)

\(^{\text{6-31g* AcProNH2, ProNH2, 6-31g*//3-21g AcProNHCH3 RLD 4/23/93}}^{\text{J}} \)
DIHEDRALS

V(dihedral) = Kchi(1 + cos(n(chi) - delta))

Kchi: kcal/mole
n: multiplicity
delta: degrees

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Parameters (dihedrals)
Parameters (improper)

IMPROPER
!
! V(incorrect) = Kpsi(ψi - ψi0)**2
!
! Kpsi: kcal/mole/rad**2
! ψi0: degrees
! note that the second column of numbers (0) is ignored
!
! atom types           Kpsi  ψi0
!
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  CPA  CPA  CPM  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 -
cutmb 14.0 cutfnb 12.0 cutmbb 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

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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
Running CHARMM

```
[madura@localhost ~]$ cd Charmm
[madura@localhost Charmm]$ ls
1qlq-jdm.pdb  bpti.ene  bpti_md.out  bpti.psf  butane.inp
1QIQ.pdb     bpti.inp   bpti_md.pdb  bpti.rst  butane.out
1qlq.seq     bpti_md.crd bpti.out   bpti.trj   butane.pdb
bpti.crd     bpti_md.inp bpti.pdb   butane.crd
[madura@localhost Charmm]$ charmm < bpti.inp > bpti.out
```
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 -
  iprfreq 100 ihtfreq 50 ieqfreq 0 inbrfl -1 ihbfreq 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

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<tr>
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<th>Time</th>
<th>TOTEnrer</th>
<th>TOTKe</th>
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<td>HFCTote</td>
<td>HFCKe</td>
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<td>ANGLEs</td>
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<td>IMPropers</td>
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<td>VIRI</td>
<td>PRESSE</td>
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</table>
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 ($\Delta G_{\text{bind}}$).

• 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.
  – *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).

```
<table>
<thead>
<tr>
<th>molecule</th>
<th>U_total</th>
<th>U_ele</th>
<th>U_vdw</th>
<th>U_ligand</th>
<th>U_solv</th>
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</table>
```
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)
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 ($k_d = 4.8 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Calculated Rate Constant (10^8 M(^{-1}) s(^{-1}))</th>
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</thead>
<tbody>
<tr>
<td>Sphere</td>
<td>148.</td>
</tr>
<tr>
<td>Sphere (no electrostatics)</td>
<td>30.6</td>
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<tr>
<td>Dumbbell</td>
<td>1.664</td>
</tr>
<tr>
<td>Flexible loop / dumbell</td>
<td>4.2</td>
</tr>
</tbody>
</table>
Bimolecular Diffusion-Controlled Rate Constant

\[
\begin{align*}
\bar{r}' &= \bar{r}_0 + \frac{DF}{k_B T} \Delta t + \bar{R} \\
\beta &= \frac{\# \text{ of hits}}{\# \text{ of trials}} \\
k &= k_D \beta [1 - \beta]^{-1} \\
k_D b &= 4\pi \frac{\int_Z e^{(U(r)/k_B T)^{-1}}}{4\pi r^2 D} \\
\Omega &= \frac{k_D}{k_D q}
\end{align*}
\]
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**

<table>
<thead>
<tr>
<th>I(M)</th>
<th>Successful Trajectories</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.71 ± 0.03</td>
</tr>
<tr>
<td>0.3</td>
<td>0.64 ± 0.02</td>
</tr>
<tr>
<td>No Electrostatics</td>
<td>0.62 ± 0.03</td>
</tr>
</tbody>
</table>
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
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, $\varepsilon_{\text{sol}}$, and the effect of ions by, $\kappa$. The solute is a set of embedded charges inside a cavity with a dielectric constant of, $\varepsilon_{\text{in}}$. 
Continuum Solvent Model

\[ \Delta G^{solv} = \Delta G^{np} + \Delta G^{elec} \]

\[ \Delta G^{np} \approx \gamma \, SA \]

\[ \Delta G^{elec} = \frac{1}{2} \sum_{i=1}^{N_{\text{atoms}}} q_i \left( \phi_i^s - \phi_i^v \right) \]
Poisson-Boltzmann Model of Molecular Electrostatics

\[-\nabla \cdot \mathbf{a} \nabla \phi_T = 4\pi \rho^f - \kappa^2 \phi \lambda\]

- Electrostatic potential
- Permittivity
- "fixed" charge density
- "masking" function
- Inverse Debye length

\[\kappa^2 = \frac{8\pi e^2 N_A I}{1000 \varepsilon k_B T}\]
Solving the FDPB Equation

• In practice, one knows the
  – charge density ($\rho$) from the fixed charges in the receptor and substrate.
  – the permittivity (dielectric constant).
  – Kappa ($\kappa$), 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

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

\( F^{Coul} \) is the Coulombic force which is the interaction of all the solute atoms with each other and is referred to as the “qE” force.

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

\( F^{DBF} \) 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.

\( F^{IBF} \) 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

\[ m \frac{d^2 x}{dt^2} = \vec{F} - m \gamma \frac{dx}{dt} + \vec{R} \]

- **mass**
- **position**
- Random fluctuations due to interactions with the solvent

Force which depends upon the position of the particle relative to the other particles

Force due to the motion through the solvent

\[ \gamma = \frac{k_B T}{mD} \]

Diffusion constant
Dichloroethane

Summary of simulation parameters

\[ \varepsilon_i = 1 \]
\[ \varepsilon_s = 80 \]
\[ \gamma = 6.5 \text{ ps}^{-1} \]
\[ dt = 0.001 \text{ ps} \]
\[ T = 1000 \text{ K} \]
grid spacing = 0.5 to 1.2 Å

<table>
<thead>
<tr>
<th>Atom Type</th>
<th>Charge (e)</th>
<th>Radius (Å)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1.82</td>
</tr>
<tr>
<td>CH₂</td>
<td>0.25</td>
<td>1.99</td>
</tr>
</tbody>
</table>

Trans conformer dominates in the gas phase

Increased gauche conformer in liquid phase
Dichloroethane

Summary of simulation results

Reference Gas Phase Results
2 ns stochastic dynamics simulation

Reference (PB solvation energies)
2 ns stochastic dynamics simulation 15 x 15 x 15 grid)
2 ns stochastic dynamics simulation 10 x 10 x 10 grid)
2 ns stochastic dynamics simulation 10 x 10 x 10, no solvent boundary forces)
Alanine “dipeptide”

Summary of simulation parameters

\[ \varepsilon_i = 1 \]
\[ \varepsilon_s = 80 \]
\[ \gamma = 6.5 \text{ ps}^{-1} \]
\[ dt = 0.001 \text{ ps} \]
\[ T = 1000 \text{ K} \]
\[ \text{grid spacing} = 0.7 \text{ to } 1.7 \text{ Å} \]

Conclusions

Good equilibration
Good agreement with other computational models
Weak sensitivity 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 $\varepsilon$ ("The Born Model")
  - *Discrete molecules* with dipoles, polarizability, etc.

![Discrete Model](image1.png) ![Continuum Model](image2.png)

Discrete Model      Continuum Model
The Born Model

- Consider: Continuum model of ion solvation.

*If medium 1 is a vacuum, $\Delta G_{\text{Born}}$ is just the free energy of solvation.*

We will calculate the free energy of transfer of an ion from medium 1 ($\varepsilon_1$) to medium 2 ($\varepsilon_2$). This will be called $\Delta G_{\text{Born}}$. 
The path for $\Delta G_{\text{born}}$ refers to:

First **discharging** the ion in medium 1 ($\Delta G_{\text{o}_1}$)

**Transferring** the ion from medium 1 to medium 2 ($G_{\text{o}_2}$)

**Recharging** the ion in solvent 2 ($\Delta G_{\text{o}_3}$)

$$\Delta G_{\text{Born}} = \Delta G_{\text{o}_1} + \Delta G_{\text{o}_2} + \Delta G_{\text{o}_3}$$
The Charging Process

- Energies of charging/discharging:
  - computed by a model where \textit{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

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 ($\Phi$) of a point charge, we have,

$$dG_{\text{charging}} = \Phi \, dq = \frac{q}{4\pi \varepsilon_0 \varepsilon_a} \, dq$$

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

\[ \Delta G_{\text{charging}} = \frac{Z^2 e^2}{8 \pi \varepsilon_0 \varepsilon_l} \]

Therefore, For \( \Delta G^0_1 \), \( \Delta G^0_2 \), and \( \Delta G^0_{\text{born}} \) we have...(Next Slide)

\[ \Delta G_{\text{discharging}} = - \Delta G_{\text{charging}} \]
The Charging Process

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)

\[
\Delta G_i^o = -\frac{Z^2 e^2}{8\pi \varepsilon_0 \varepsilon_i a}
\]

\[
\Delta G_2^o = +\frac{Z^2 e^2}{8\pi \varepsilon_0 \varepsilon_2 a}
\]

\[
\Delta G_{\text{Born}}^o = \frac{Z^2 e^2}{8\pi \varepsilon_0 a} \left( \frac{1}{\varepsilon_2} - \frac{1}{\varepsilon_1} \right) + \Delta G_2^o
\]
Free Energy of Solvation

• Consider: Transferring an ion from a vacuum to a medium of $\varepsilon$.
  – Assume $\Delta G^o_2 = 0$. (No interaction between solvent and discharged ion).

$$\Delta G^o_{\text{solution}} = \frac{Z^2 e^2}{8\pi \varepsilon_0 a} \left( \frac{1}{\varepsilon} - 1 \right)$$

Two points to note:
1. $\Delta G < 0$ if $\varepsilon > 1$
2. $\Delta G$ 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 $\varepsilon$.

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

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

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

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

\[ f(r_{ij}, a_{ij}) = \sqrt{r_{ij}^2 + a_{ij}^2 e^{-D}} \]

\[ a_{ij} = \sqrt{a_i a_j} \quad D = \frac{r_{ij}^2}{\left(2a_{ij}\right)^2} \]
Generalized Born

• Note the following
  – When $i=j$ the equation returns the Born expression
  – When $r_{ij} \ll a_i$ and $a_j$ the expression is close to the Onsager result (i.e. a dipole)
  – When $r_{ij} \gg a_i$ 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
ΔEE = ΔG = -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

\[ R + S \iff R : S \]

• Where R represents to receptor, S represents the substrate and R:S is the noncovalent complex.

• The binding free energy can be partitioned into

\[
\Delta G = \Delta G_s (R : S) - \Delta G_s (R) - \Delta G_s (S) + \Delta G_a + \Delta G_n
\]
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

<table>
<thead>
<tr>
<th>Protein</th>
<th>$\Delta\Delta G_s$</th>
<th>$\Delta\Delta G_a$</th>
<th>$\Delta\Delta G_{\text{calc}}$</th>
<th>$\Delta\Delta G_{\text{expt}}$</th>
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<td>4.2</td>
<td>3.8</td>
<td>4.8</td>
</tr>
</tbody>
</table>
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.