Force Fields for Classical Molecular Dynamics simulations of Biomolecules

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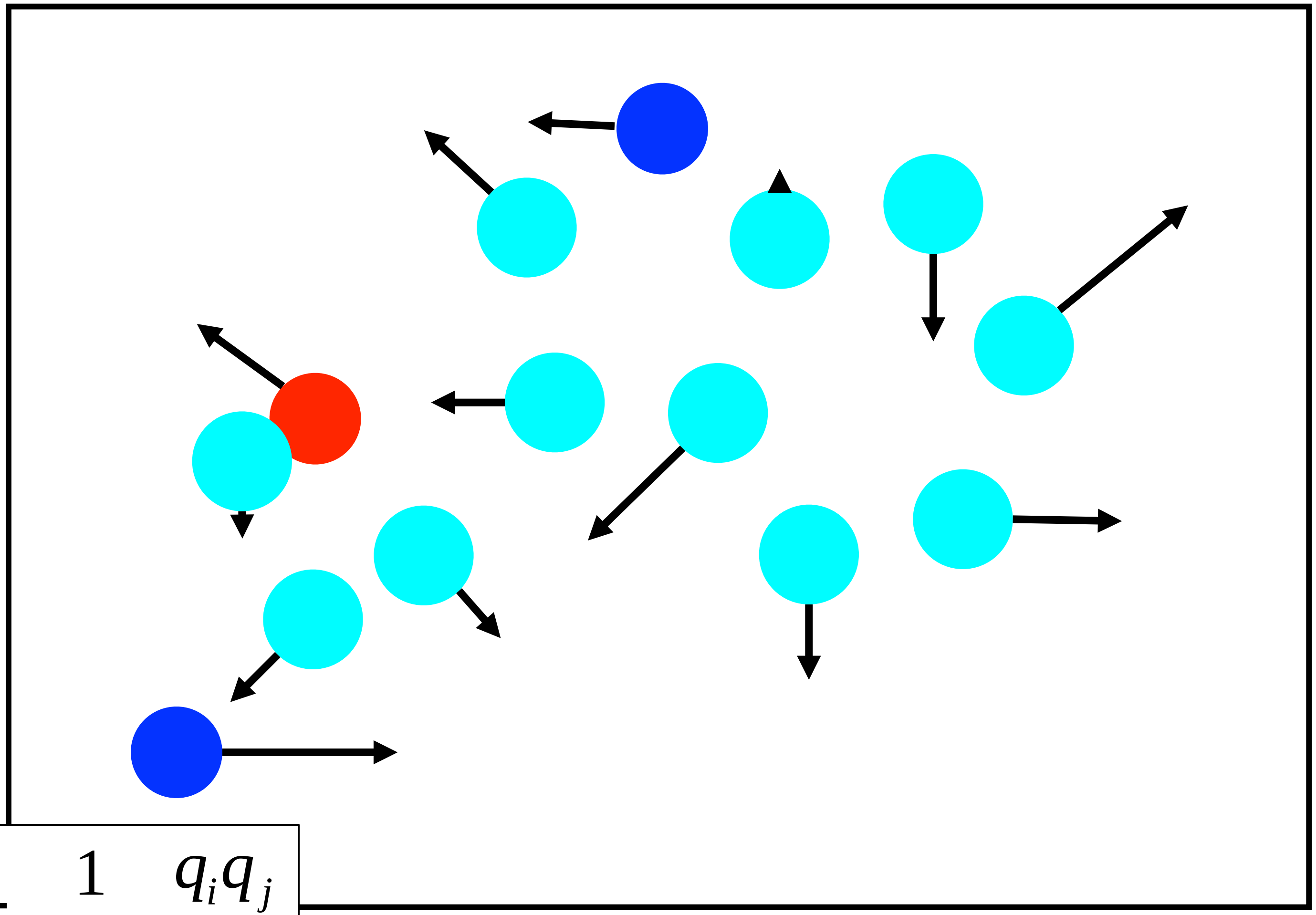
Classical Force Field Parameters

- Topology and structure files
- Parameter files
- Where do all the numbers needed by an MD code come from?
- Where to find these numbers and how to change them if needed.
- How to make topology files for ligands, cofactors, special amino acids, …
- How to develop / put together missing parameters.

Classical Molecular Dynamics

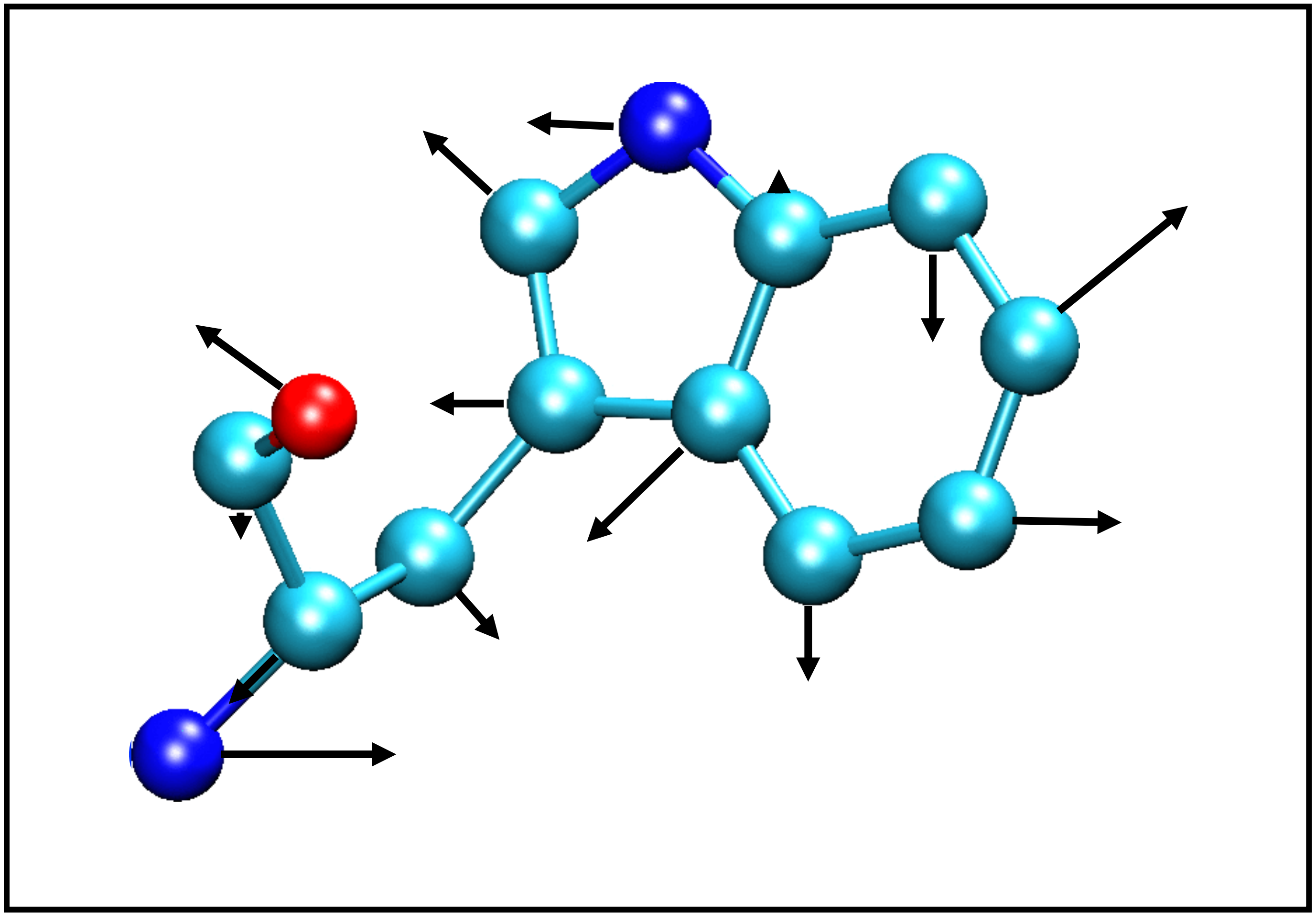


$$U(r) = \frac{1}{4\pi\varepsilon_0}\frac{q_i q_j}{r_{ij}}$$

Coulomb interaction

$$U(r) = \epsilon_{ij}[(\frac{R_{min,ij}}{r_{ij}})^{12} - (\frac{R_{min,ij}}{r_{ij}})^{6}]$$

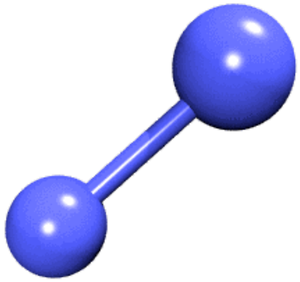
Classical Molecular Dynamics



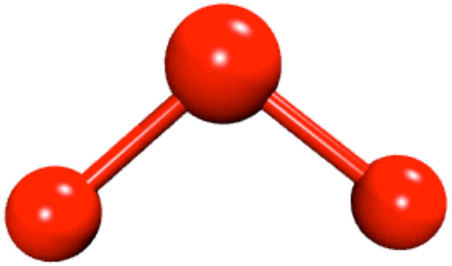
Bond definitions, atom types, atom names, parameters, ….

Energy Terms Described in

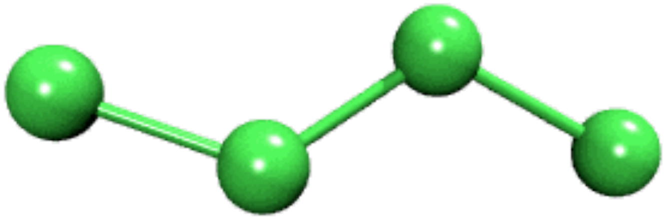
Bond



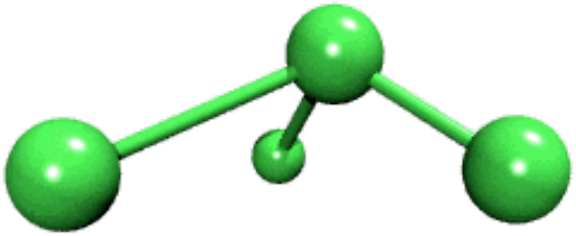
Angle



Dihedral



Improper



The Potential Energy Function

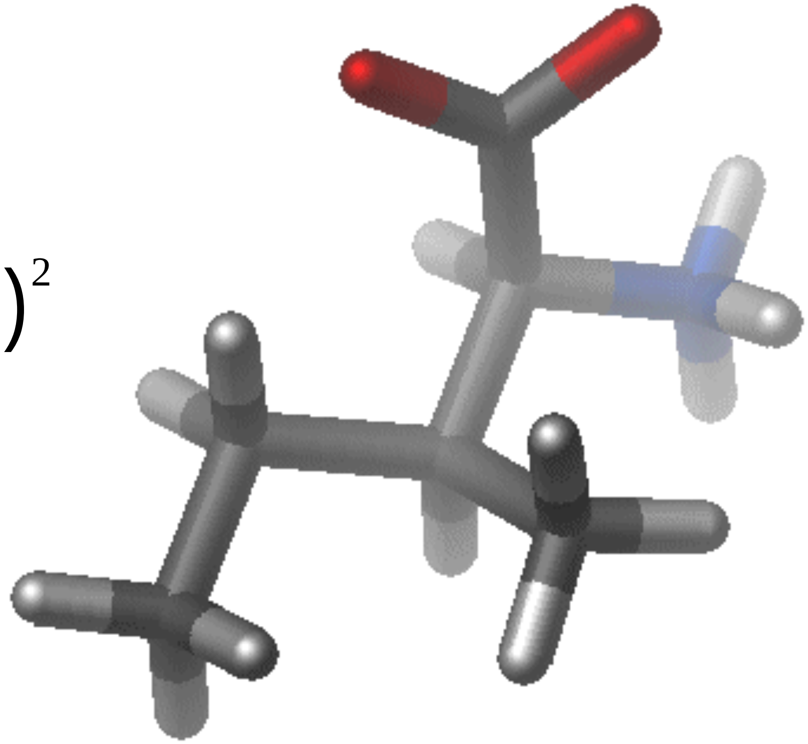
$$
\begin{aligned}
U(\vec{R}) \quad = \quad & \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} + \\
& \underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} + \\
& \underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}
\end{aligned}
$$

U_{bond} = oscillations about the equilibrium bond length
U_{angle} = oscillations of 3 atoms about an equilibrium bond angle
$U_{dihedral}$ = torsional rotation of 4 atoms about a central bond
$U_{nonbond}$ = non-bonded energy terms (electrostatics and Lenard-Jones)

Interactions between bonded atoms

$$V_{angle} = K_{\theta}\left(\theta - \theta_o\right)^2$$

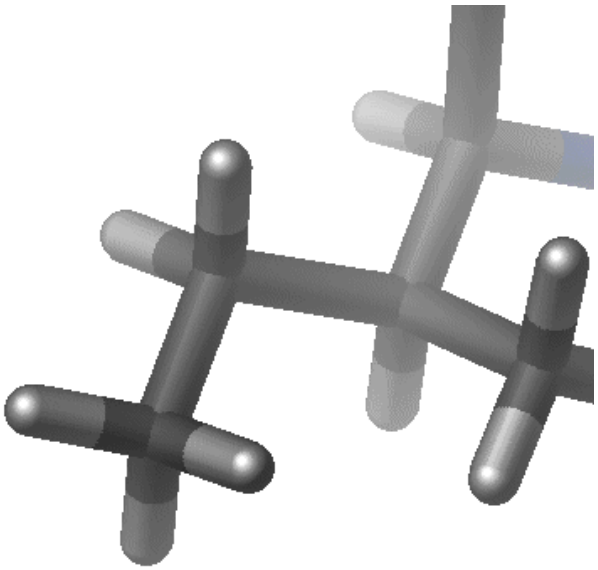
$$V_{bond} = K_b\left(b - b_o\right)^2$$

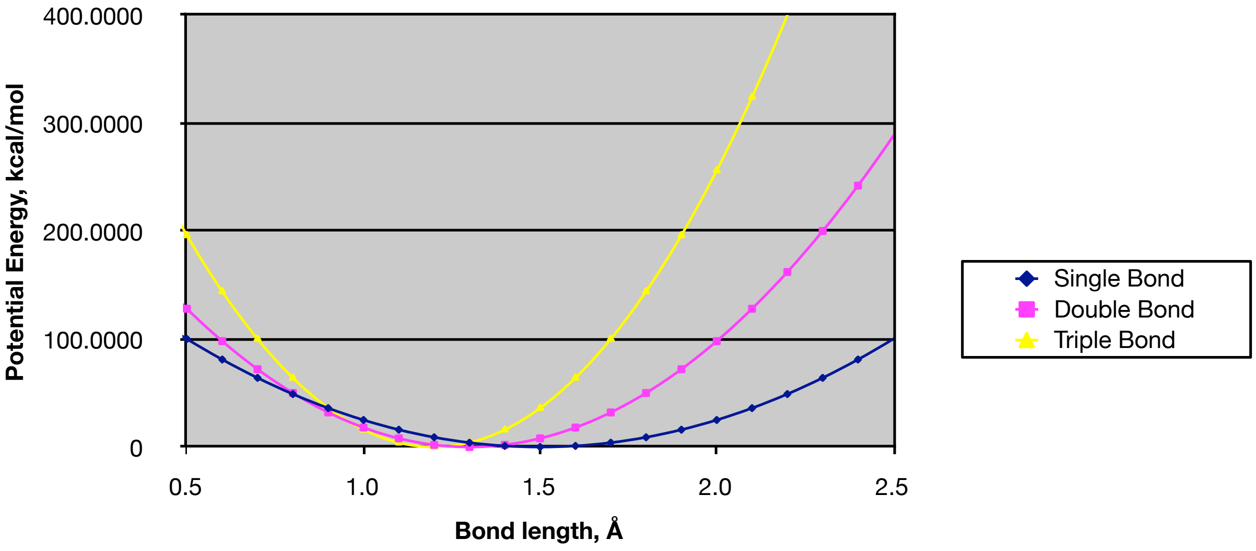


$$V_{dihedral} = K_{\phi}(1 + \cos(n\phi - \delta))$$

$$V_{bond} = K_b \left(b - b_o\right)^2$$

Chemical type	K_{bond}	b_o
C-C	100 kcal/mole/Å ^{2}	1.5 Å
C=C	200 kcal/mole/Å ^{2}	1.3 Å
C≡C	400 kcal/mole/Å ^{2}	1.2 Å

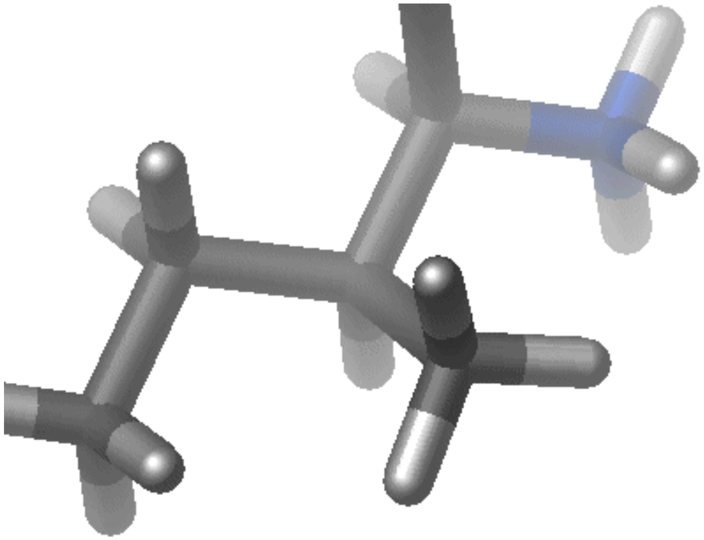




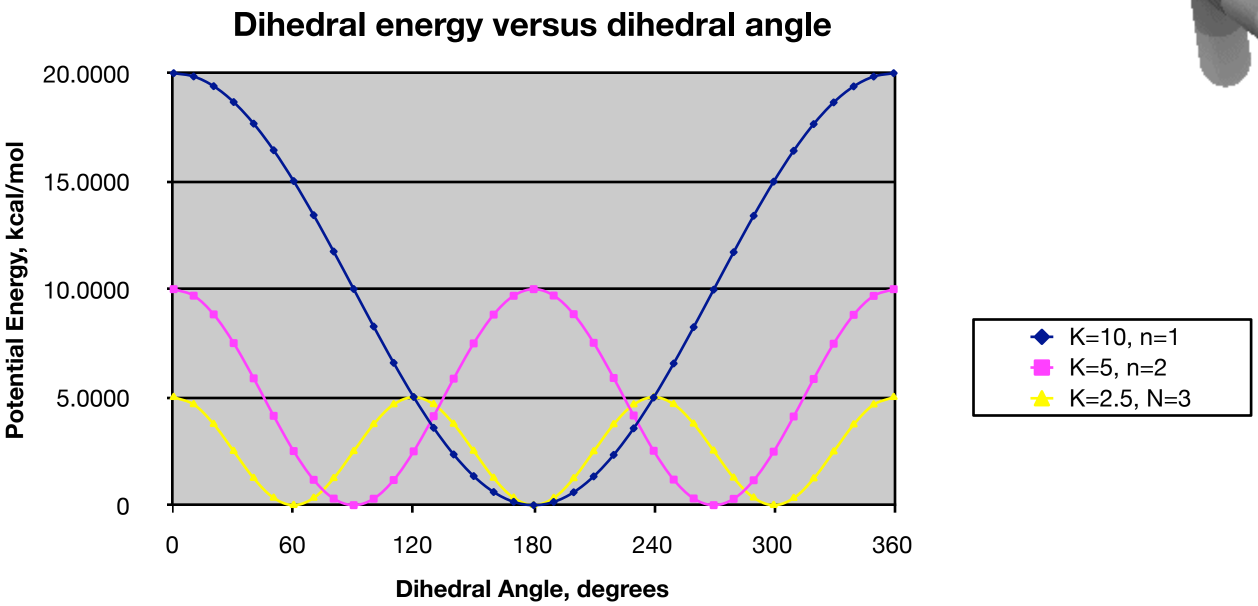
Bond Energy versus Bond length

Bond angles and *improper* terms have similar quadratic forms, but with softer spring constants. The force constants can be obtained from vibrational analysis of the molecule (experimentally or theoretically).

Dihedral Potential



$$V_{dihedral} = K_{\phi}(1+\cos(n\phi-\delta))$$



$\delta = 0^{\circ}$

Nonbonded Parameters

$$\sum_{\mathrm{non-bonded}} \frac{q_i q_j}{4\pi D r_{ij}} + \epsilon_{ij}[(\frac{R_{min,ij}}{r_{ij}})^{12} - (\frac{R_{min,ij}}{r_{ij}})^{6}]$$

q_i: partial atomic charge

D: dielectric constant

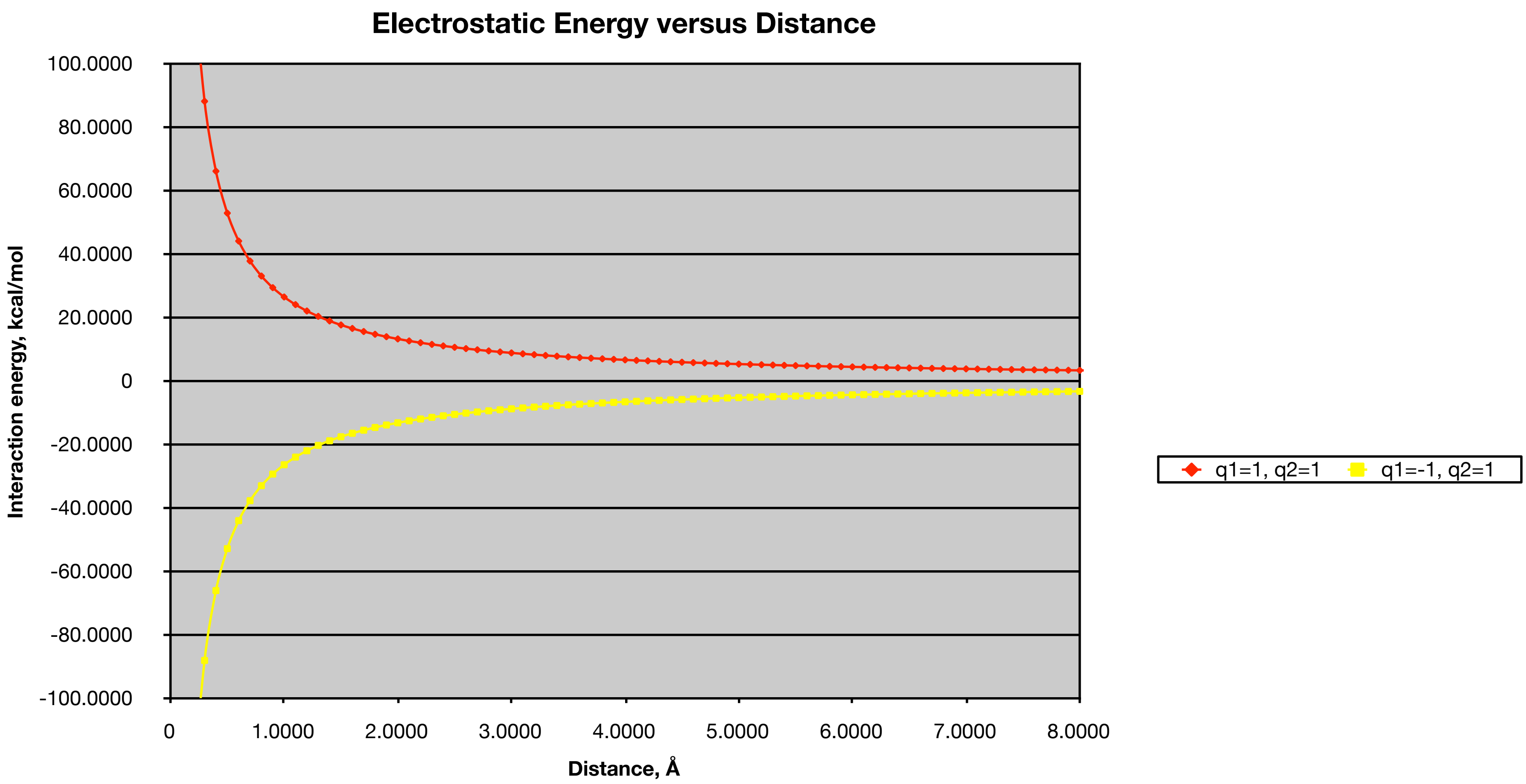
ε: Lennard-Jones (LJ, vdW) well-depth

R_{min}: LJ radius (R_{min}/2 in CHARMM)

Combining rules (CHARMM, Amber)

$R_{min\ i,j} = R_{min\ i} + R_{min\ j}$

$\varepsilon_{i,j} = \mathrm{SQRT}(\varepsilon_i * \varepsilon_j)$



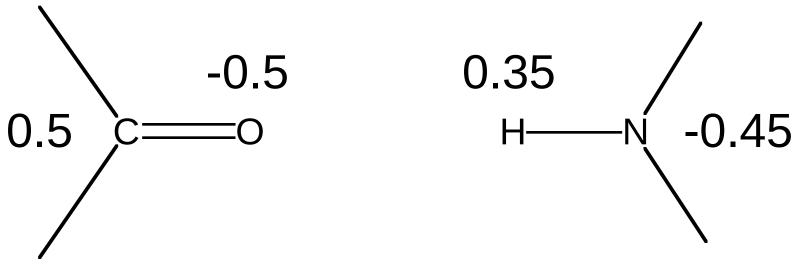
Note that the effect is long range.

From MacKerell

Charge Fitting Strategy

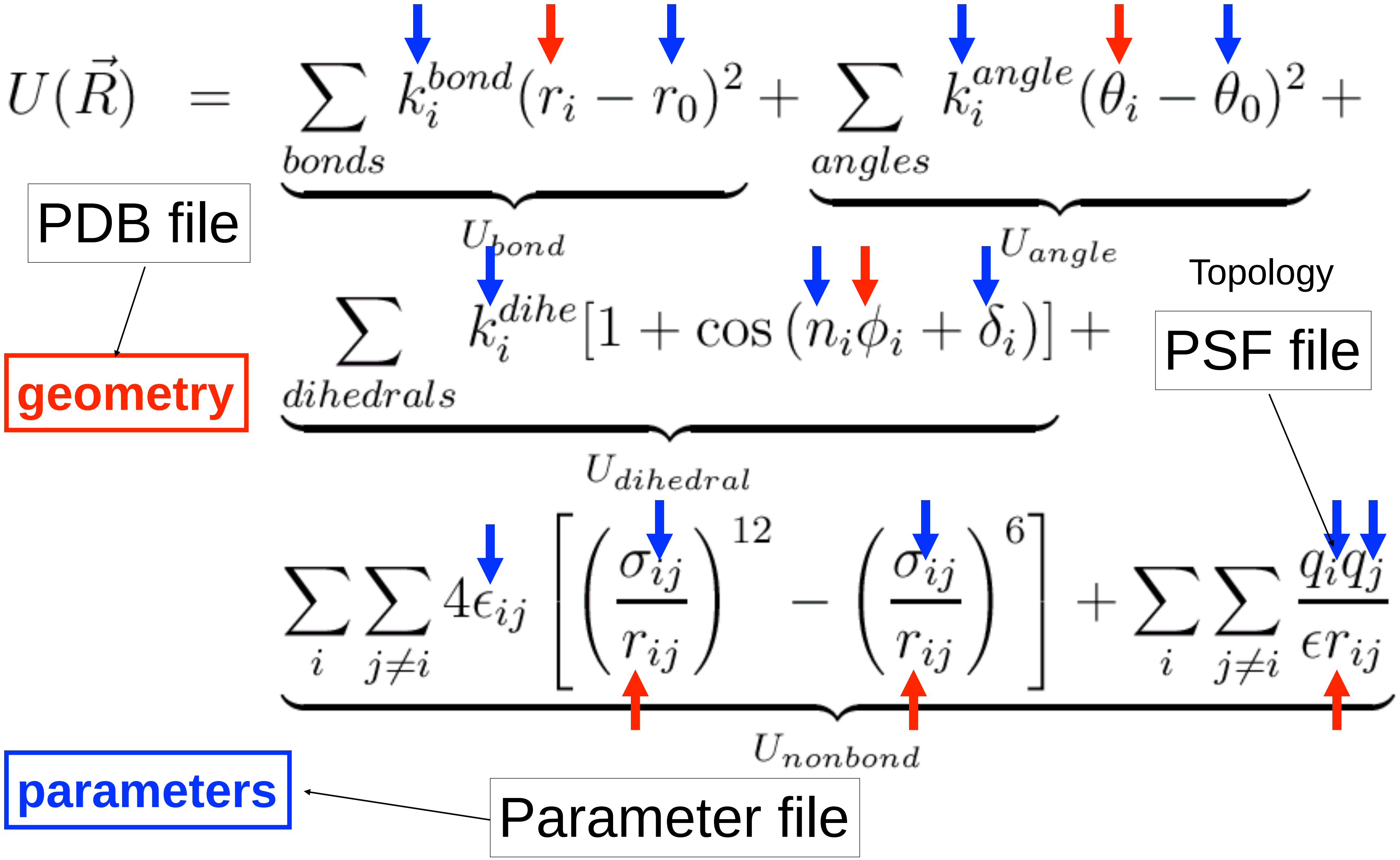
CHARMM- Mulliken* AMBER(ESP/RESP)

Partial atomic charges



*Modifications based on interactions with TIP3 water

CHARMM Potential Function



$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} +$$

$$\underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} +$$

$$\underbrace{\sum_i \sum_{j\neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j\neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}$$

PDB file

geometry

Topology

PSF file

parameters

Parameter file

File Format/Structure

- The structure of a pdb file
- The structure of a psf file
- The topology file
- The parameter file
- Connection to potential energy terms

Structure of a PDB file

index

name

resname

chain

resid

x

y

z

segname

```
ATOM     22  N   ALA B   3      -4.073  -7.587  -2.708  1.00  0.00      BH
ATOM     23  HN  ALA B   3      -3.813  -6.675  -3.125  1.00  0.00      BH
ATOM     24  CA  ALA B   3      -4.615  -7.557  -1.309  1.00  0.00      BH
ATOM     25  HA  ALA B   3      -4.323  -8.453  -0.704  1.00  0.00      BH
ATOM     26  CB  ALA B   3      -4.137  -6.277  -0.676  1.00  0.00      BH
ATOM     27  HB1 ALA B   3      -3.128  -5.950  -0.907  1.00  0.00      BH
ATOM     28  HB2 ALA B   3      -4.724  -5.439  -1.015  1.00  0.00      BH
ATOM     29  HB3 ALA B   3      -4.360  -6.338   0.393  1.00  0.00      BH
ATOM     30  C   ALA B   3      -6.187  -7.538  -1.357  1.00  0.00      BH
ATOM     31  O   ALA B   3      -6.854  -6.553  -1.264  1.00  0.00      BH
ATOM     32  N   ALA B   4      -6.697  -8.715  -1.643  1.00  0.00      BH
ATOM     33  HN  ALA B   4      -6.023  -9.463  -1.751  1.00  0.00      BH
ATOM     34  CA  ALA B   4      -8.105  -9.096  -1.934  1.00  0.00      BH
ATOM     35  HA  ALA B   4      -8.287  -8.878  -3.003  1.00  0.00      BH
ATOM     36  CB  ALA B   4      -8.214 -10.604  -1.704  1.00  0.00      BH
ATOM     37  HB1 ALA B   4      -7.493 -11.205  -2.379  1.00  0.00      BH
ATOM     38  HB2 ALA B   4      -8.016 -10.861  -0.665  1.00  0.00      BH
ATOM     39  HB3 ALA B   4      -9.245 -10.914  -1.986  1.00  0.00      BH
ATOM     40  C   ALA B   4      -9.226  -8.438  -1.091  1.00  0.00      BH
ATOM     41  O   ALA B   4     -10.207  -7.958  -1.667  1.00  0.00      BH
00000000000000000000000000000000000000000000000000000000000000000000000000
        10        20        30         40         50         60         70
```

>>> It is an ascii, fixed-format file <<<

"No connectivity information"

Looking at File Structures

- PDB file
- Topology file
- PSF file
- Parameter file

Parameter Optimization Strategies

Check if it has been parameterized by somebody else

- Literature
- Google

Minimal optimization

- By analogy (direct transfer of known parameters)
- Quick, starting point

Maximal optimization

- Time-consuming
- Requires appropriate experimental and target data

Choice based on goal of the calculations

- Minimal
  - database screening
  - NMR/X-ray structure determination
- Maximal
  - free energy calculations, mechanistic studies, subtle environmental effects

Getting Started

- Identify previously parameterized compounds
- Access topology information – assign atom types, connectivity, and charges – annotate changes

CHARMM topology (parameter files)

top_all22_model.inp (par_all22_prot.inp)
top_all22_prot.inp (par_all22_prot.inp)
top_all22_sugar.inp (par_all22_sugar.inp)
top_all27_lipid.rtf (par_all27_lipid.prm)
top_all27_na.rtf (par_all27_na.prm)
top_all27_na_lipid.rtf (par_all27_na_lipid.prm)
top_all27_prot_lipid.rtf (par_all27_prot_lipid.prm)
top_all27_prot_na.rtf (par_all27_prot_na.prm)
toph19.inp (param19.inp)

NA and lipid force fields have new LJ parameters for the alkanes, representing increased optimization of the protein alkane parameters. Tests have shown that these are compatible (e.g. in protein-nucleic acid simulations). For new systems is suggested that the new LJ parameters be used. Note that only the LJ parameters were changed; the internal parameters are identical

www.pharmacy.umaryland.edu/faculty/amackere/force_fields.htm

Partial Charge Assignment

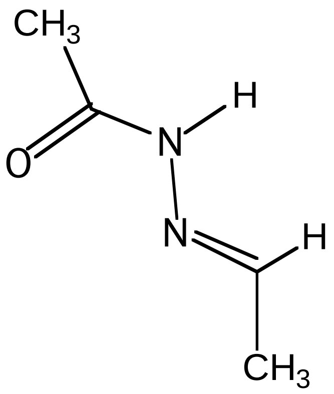
- Most important aspect for ligands

- Different force fields might take different philosophies
  - AMBER: RESP charges at the HF/6-31G level
    - Overestimation of dipole moments
    - Easier to set up
  - CHARMM: Interaction based optimization
    - TIP3P water representing the environment
    - Could be very difficult to set up

- Conformation dependence of partial charges
- Lack of polarization

- Try to be consistent within the force field

- pKa calculations for titratable residues



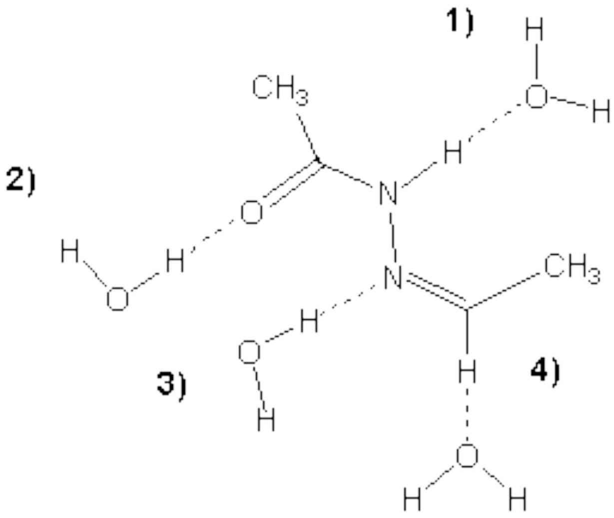
Starting charges??

Mulliken population analysis

Analogy comparison

Final charges (methyl, vary q_C to maintain integer charge, q_H = 0.09)

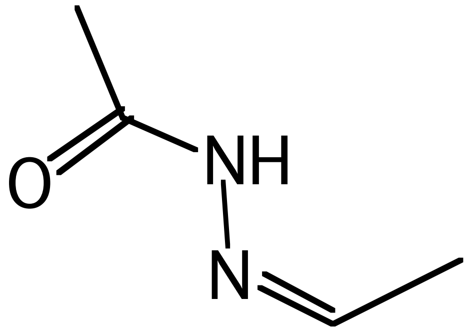
interactions with water (HF/6-31G*, monohydrates!)



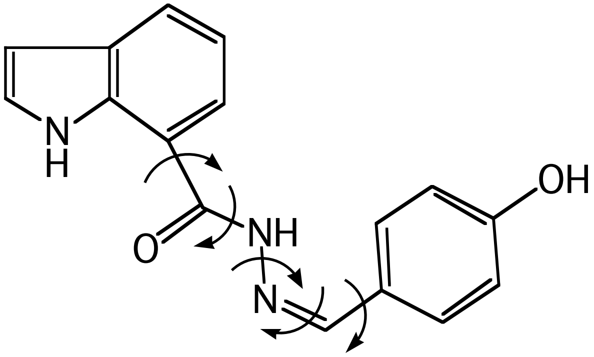
From MacKerell

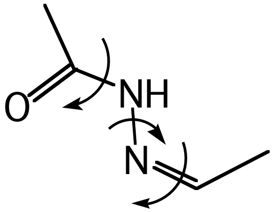
Comparison of analogy and optimized charges

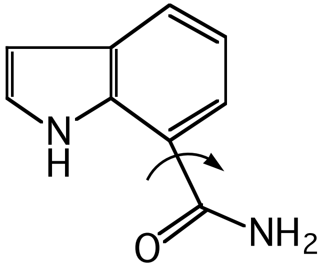
Name	Type	Analogy	Optimized
C1	CT3	-0.27	-0.27
H11	HA3	0.09	0.09
H12	HA3	0.09	0.09
H13	HA3	0.09	0.09
C2	C	0.51	0.58
O2	O	-0.51	-0.50
N3	NH1	-0.47	-0.32
H3	H	0.31	0.33
N4	NR1	0.16	-0.31
C5	CEL1	-0.15	-0.25
H51	HEL1	0.15	0.29
C6	CT3	-0.27	-0.09
H61	HA	0.09	0.09
H62	HA	0.09	0.09
H63	HA	0.09	0.09

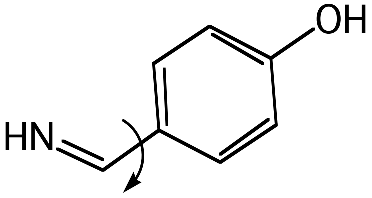


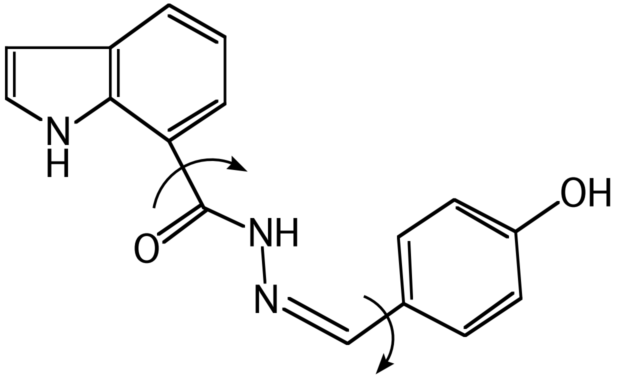
Dihedral optimization based on QM potential energy surfaces (HF/6-31G* or MP2/6-31G*).







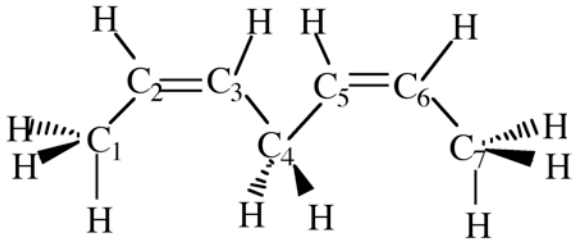


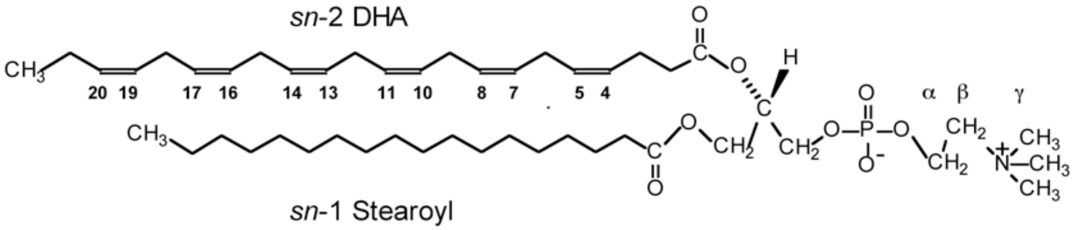


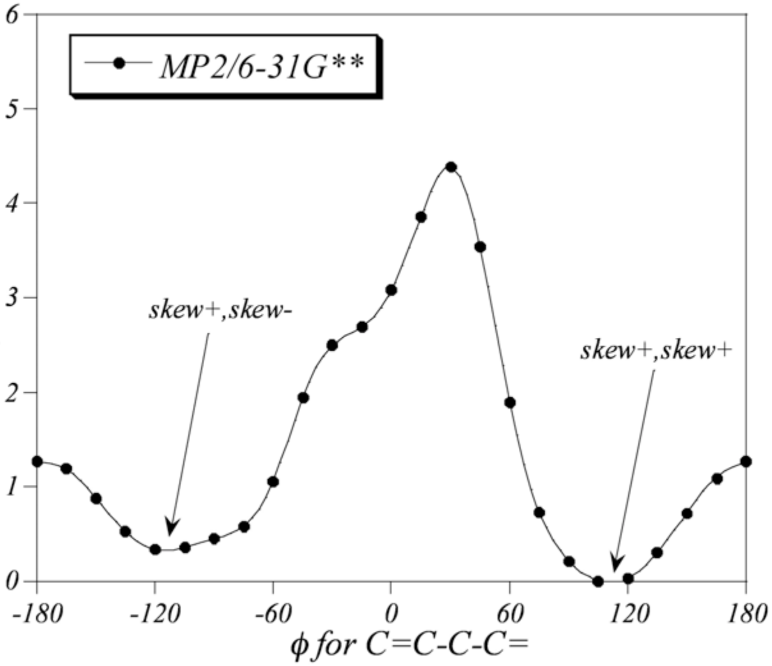
From MacKerell

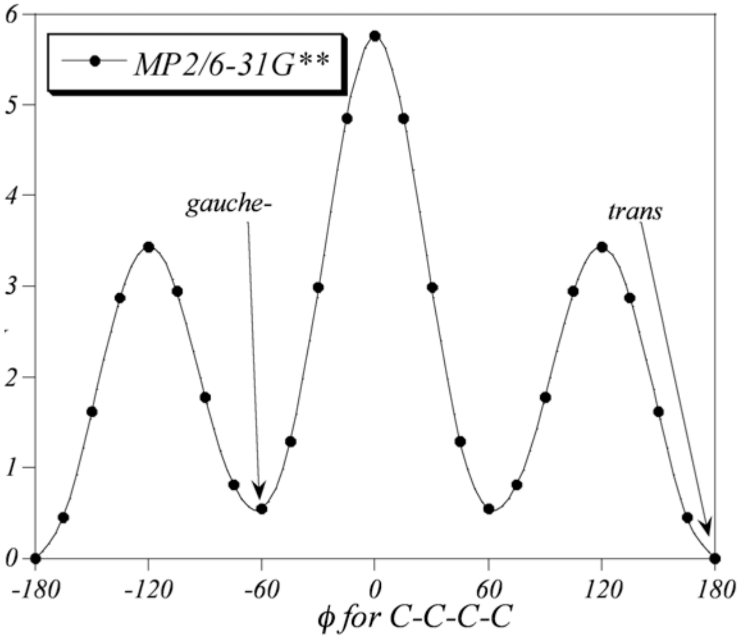
Parameterization of unsaturated lipids

- All C=C bonds are cis, what does rotation about neighboring single bonds look like?





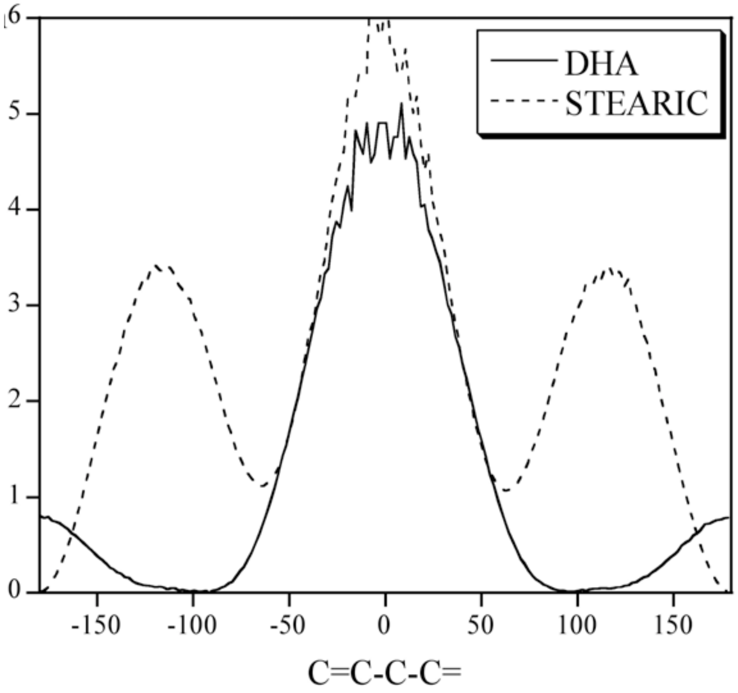


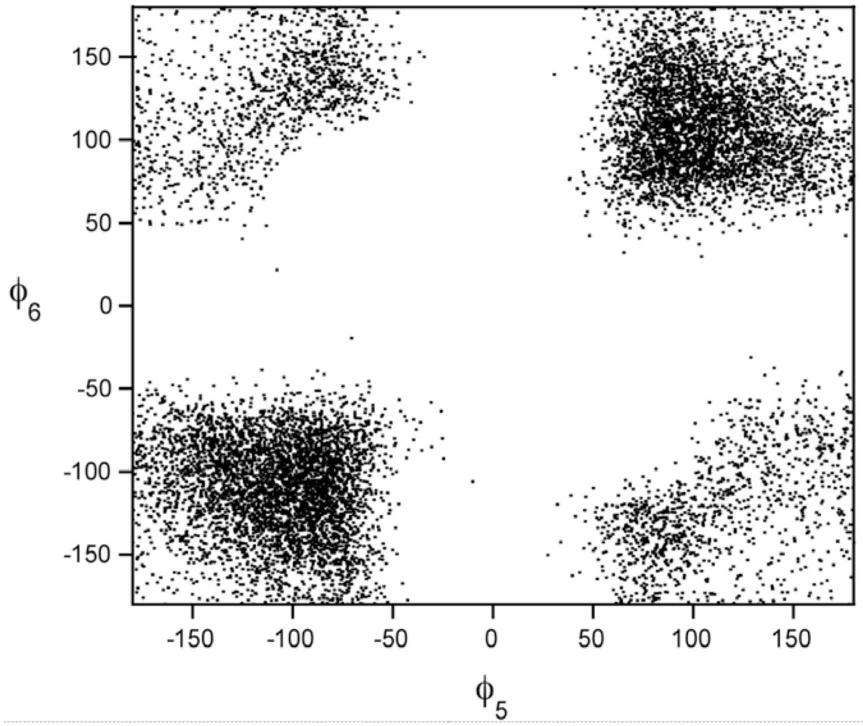


Courtesy of Scott Feller, Wabash College

DHA conformations from MD

- rotational barriers are extremely small
- many conformers are accessible w/ short lifetimes

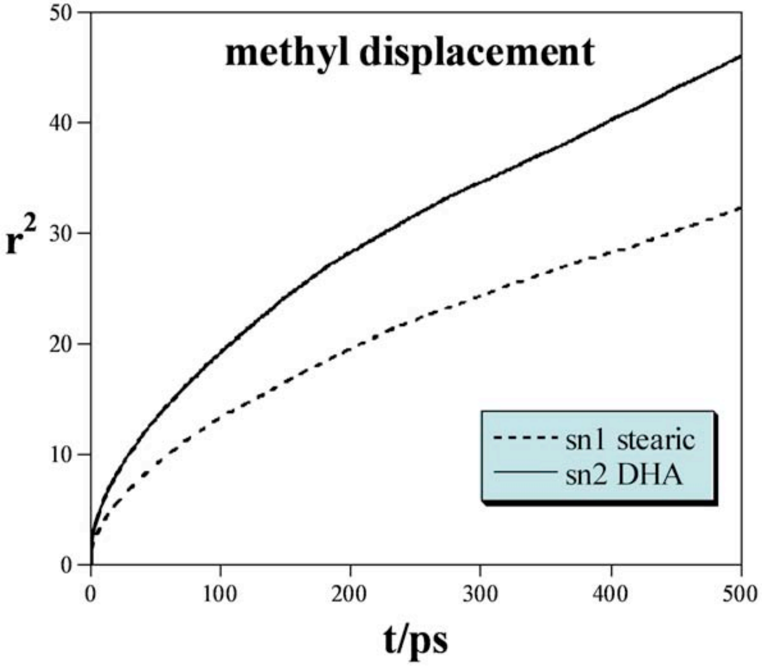


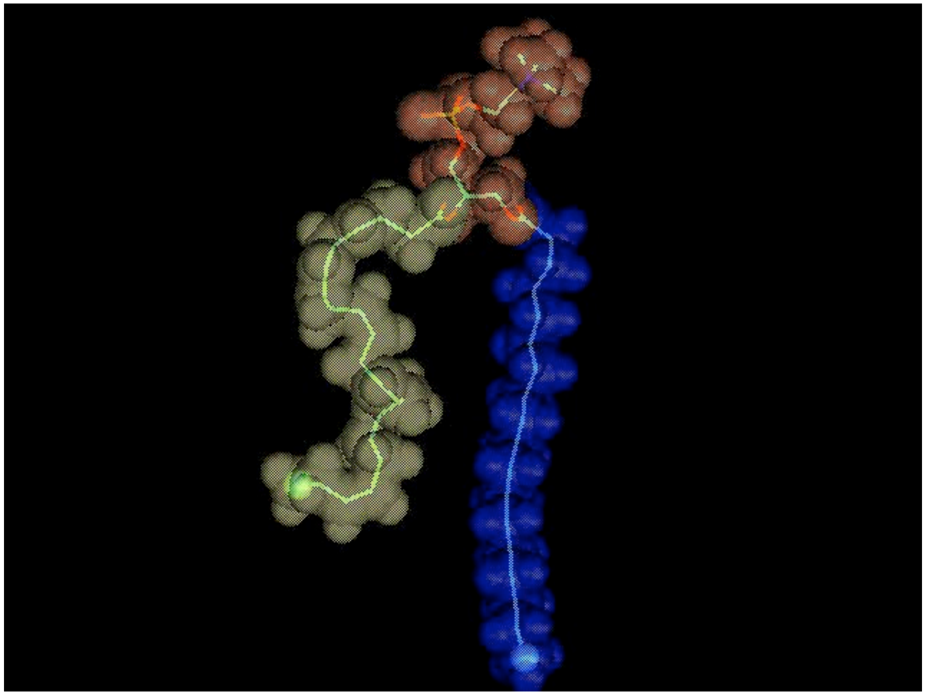


Courtesy of Scott Feller, Wabash College

Dynamics of saturated vs. polyunsaturated lipid chains

- *sn*1 stearic acid = blue
- *sn*2 DHA = yellow
- 500 ps of dynamics



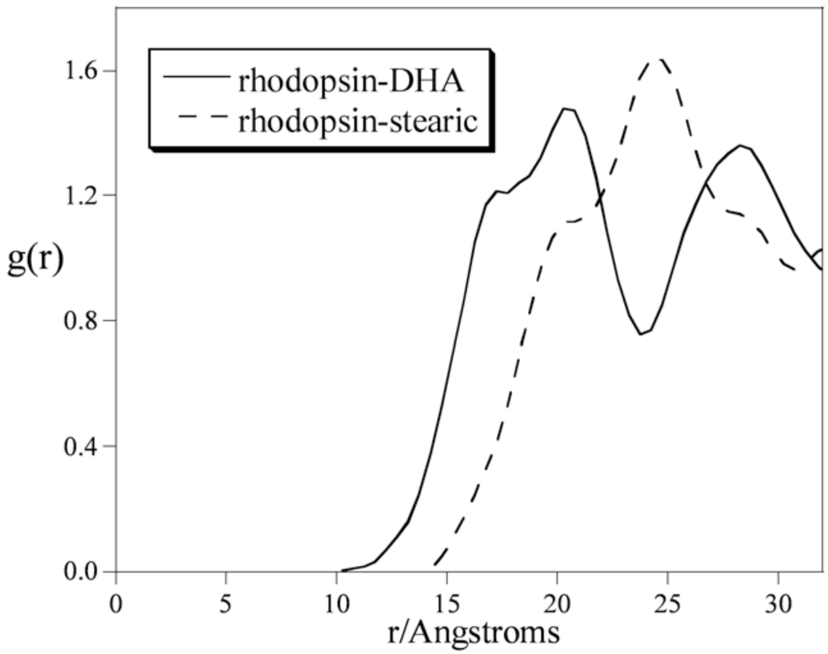


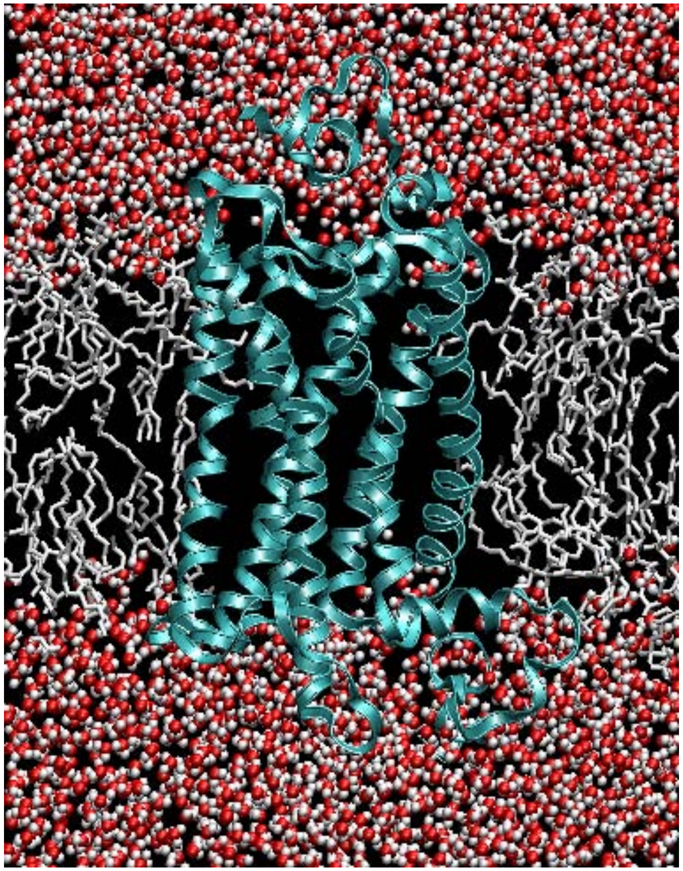
Movie courtesy of Mauricio Carrillo Tripp

Courtesy of Scott Feller, Wabash College

Lipid-protein interactions

- Radial distribution around protein shows distinct layering of acyl chains

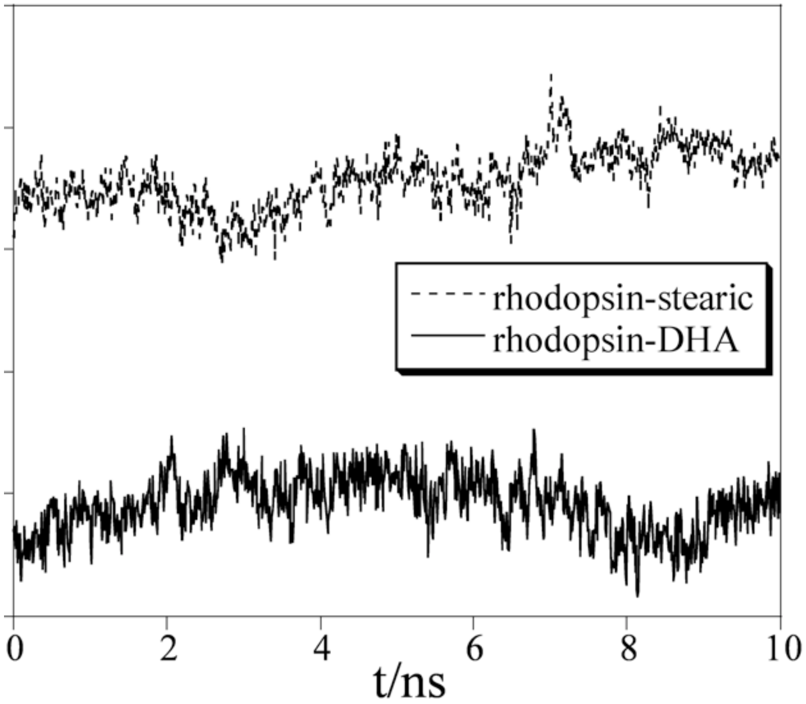




Courtesy of Scott Feller, Wabash College

Lipid-protein interactions

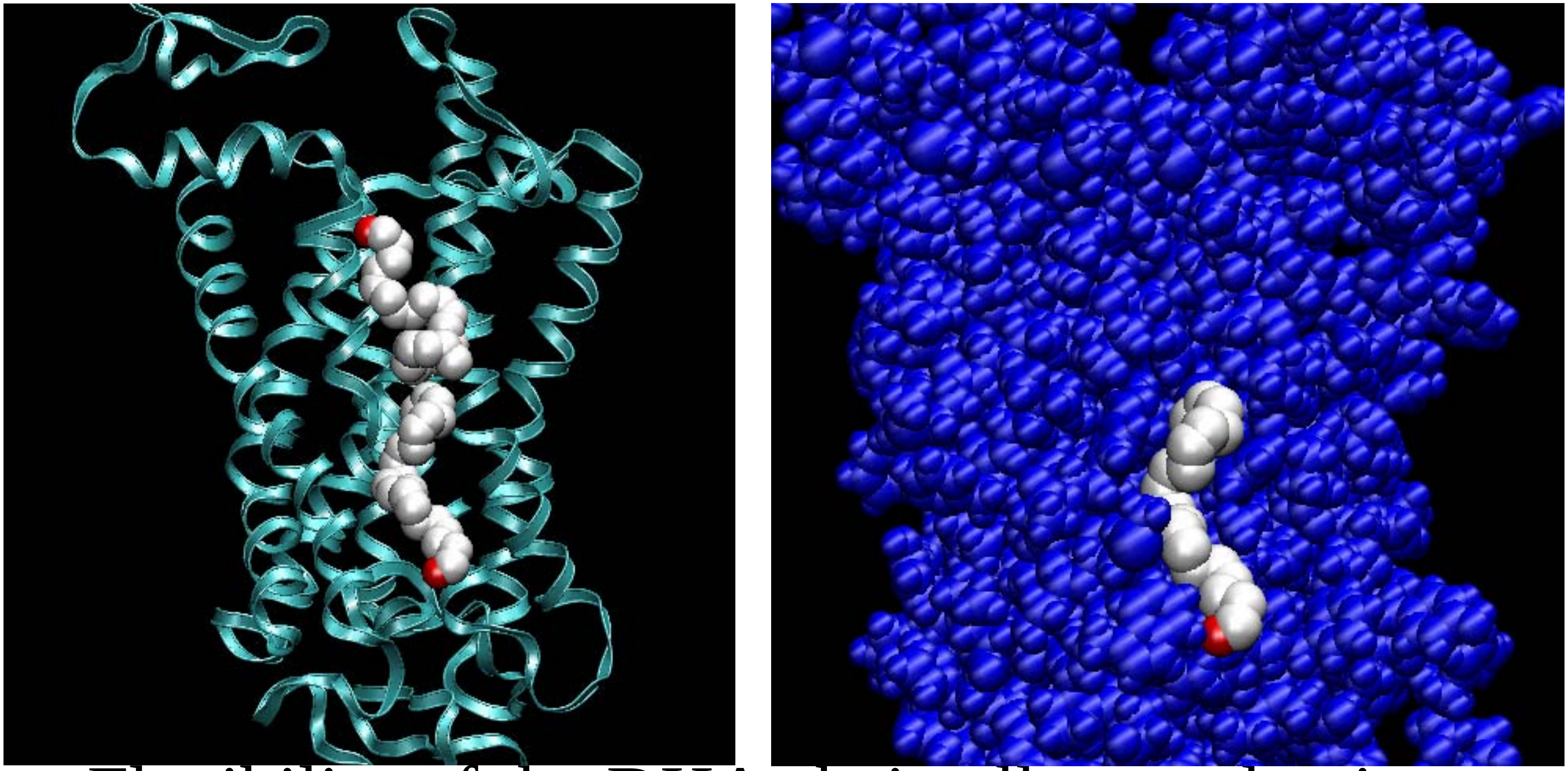
- Decomposition of non-bonded interaction shows rhodopsin is strongly attracted to unsaturated chain
- All hydrophobic residues are stabilized by DHA



resname	U_{DHA}	$U_{stearic}$	ratio
PHE	-44.9	-22.6	2.0
ILE	-30.0	-10.1	3.0
VAL	-24.0	-9.6	2.5
LEU	-23.1	-13.0	1.8
MET	-22.8	-9.7	2.4
TYR	-18.6	-10.4	1.8
ALA	-11.4	-3.0	3.8
TRP	-10.3	-2.4	4.2

Courtesy of Scott Feller, Wabash College

Origin of protein:DHA attraction



- Flexibility of the DHA chain allows solvation of the rough protein surface to occur with little intra-molecular energy cost

Courtesy of Scott Feller, Wabash College

Major Recent Developments

- New set of lipid force field parameters for CHARMM (CHARMM32$^+$)
  - Pastor, B. Brooks, MacKerell

- Polarizable force field
  - Roux, MacKerell