Force Fields for Classical Molecular Dynamics simulations of Biomolecules

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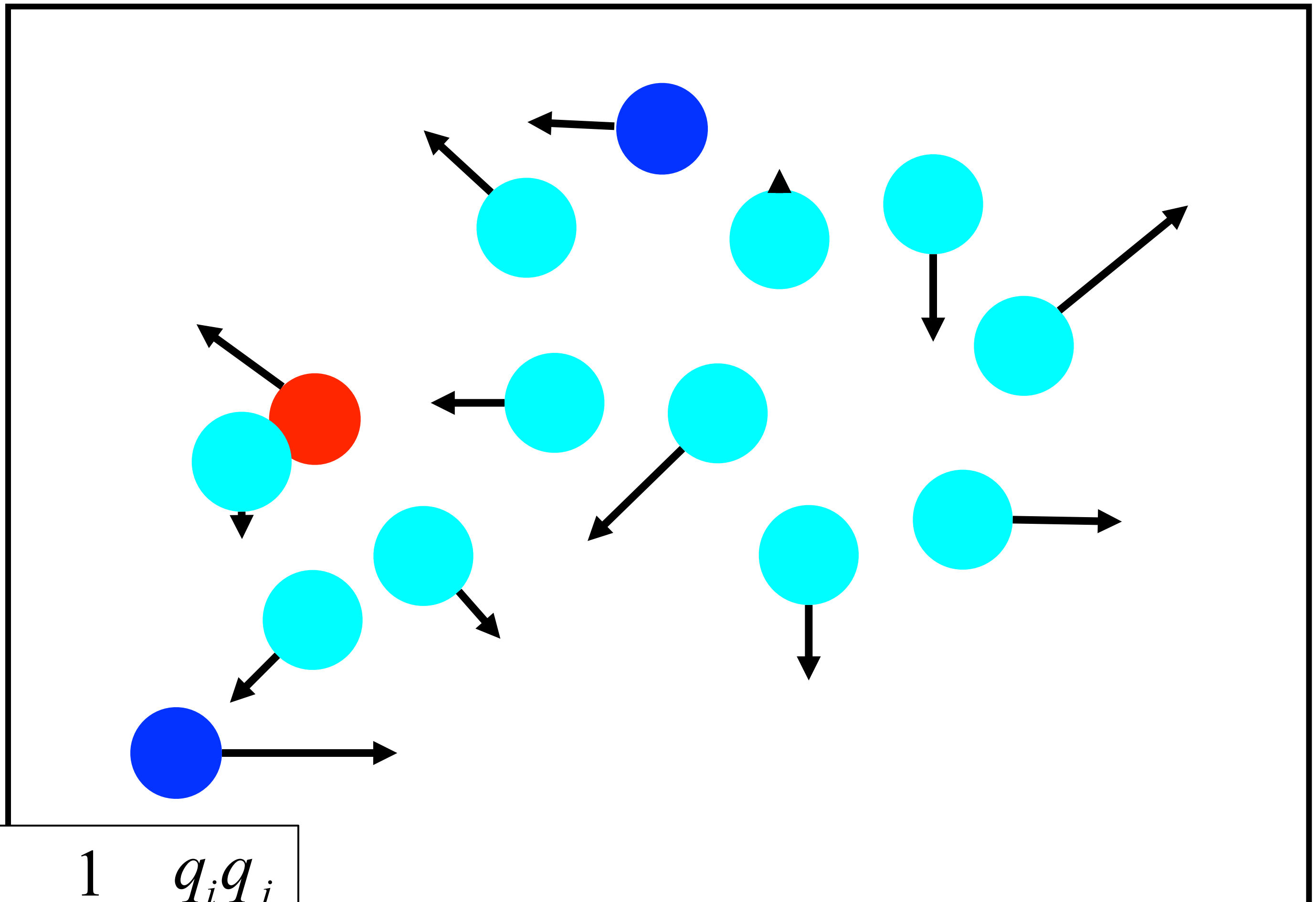
Classical Force Field Parameters

- 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

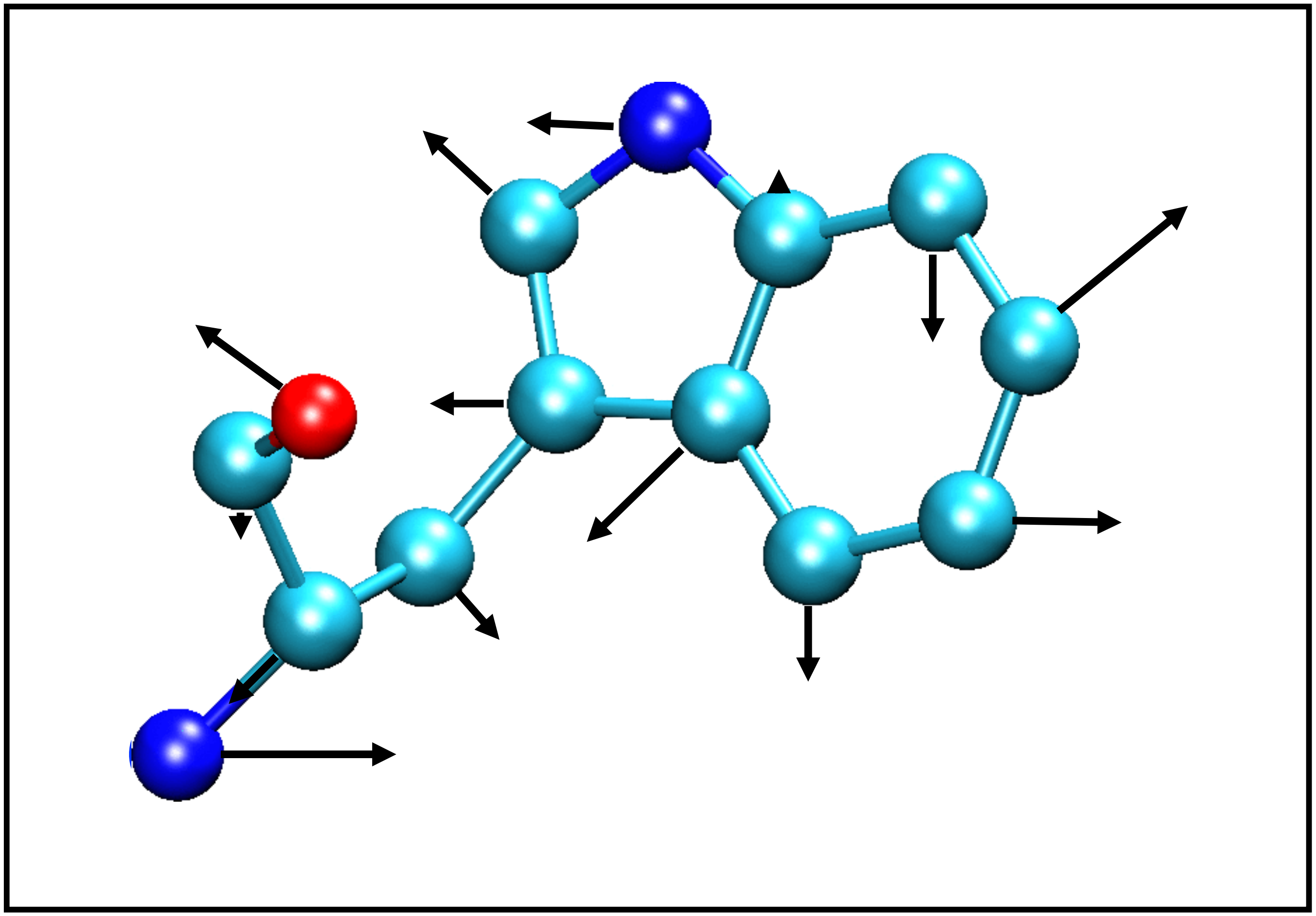


$$U(r) = \frac{1}{4\pi\varepsilon_0}\frac{q_i q_j}{r_{ij}}$$

Coulomb interaction

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

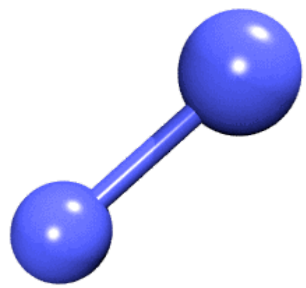
Classical Molecular Dynamics



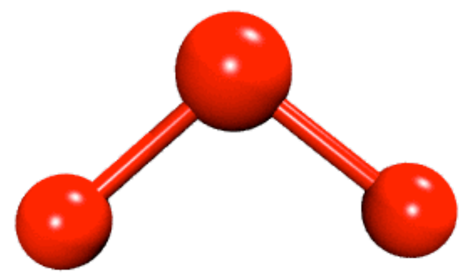
Bond definitions, atom types, atom names, parameters, ….

Energy Terms Described in

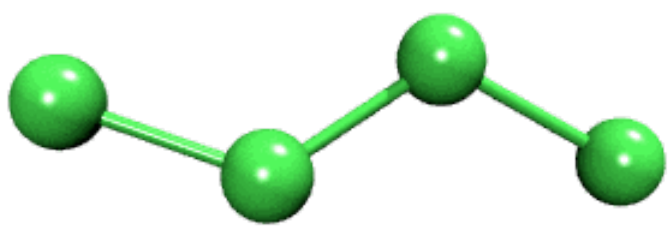
Bond



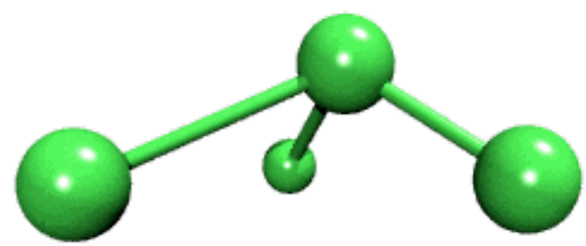
Angle



Dihedral



Improper



The Potential Energy Function

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

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

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

U_{bond} = oscillations about the equilibrium bond length

U_{angle} = oscillations of 3 atoms about an equilibrium bond angle

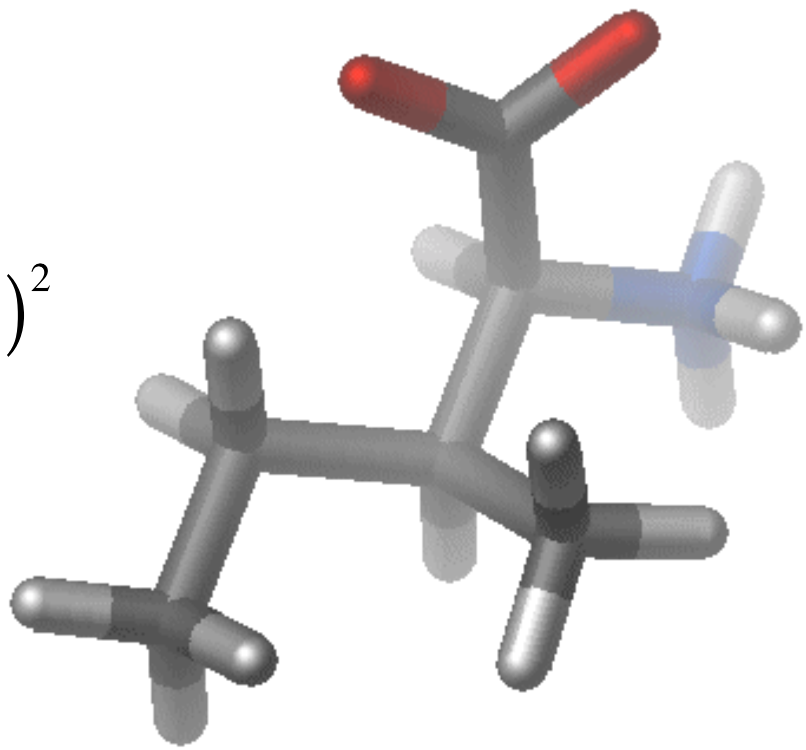
$U_{dihedral}$ = torsional rotation of 4 atoms about a central bond

$U_{nonbond}$ = non-bonded energy terms (electrostatics and Lenard-Jones)

Interactions between bonded atoms

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

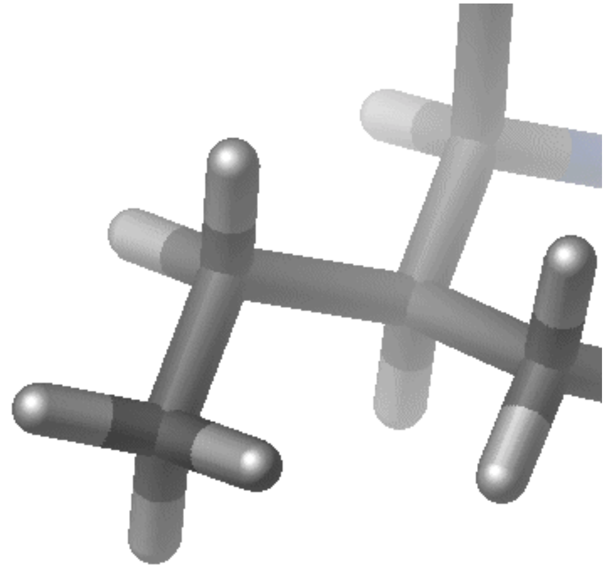
$$V_{bond} = K_b\left(b - b_o\right)^2$$

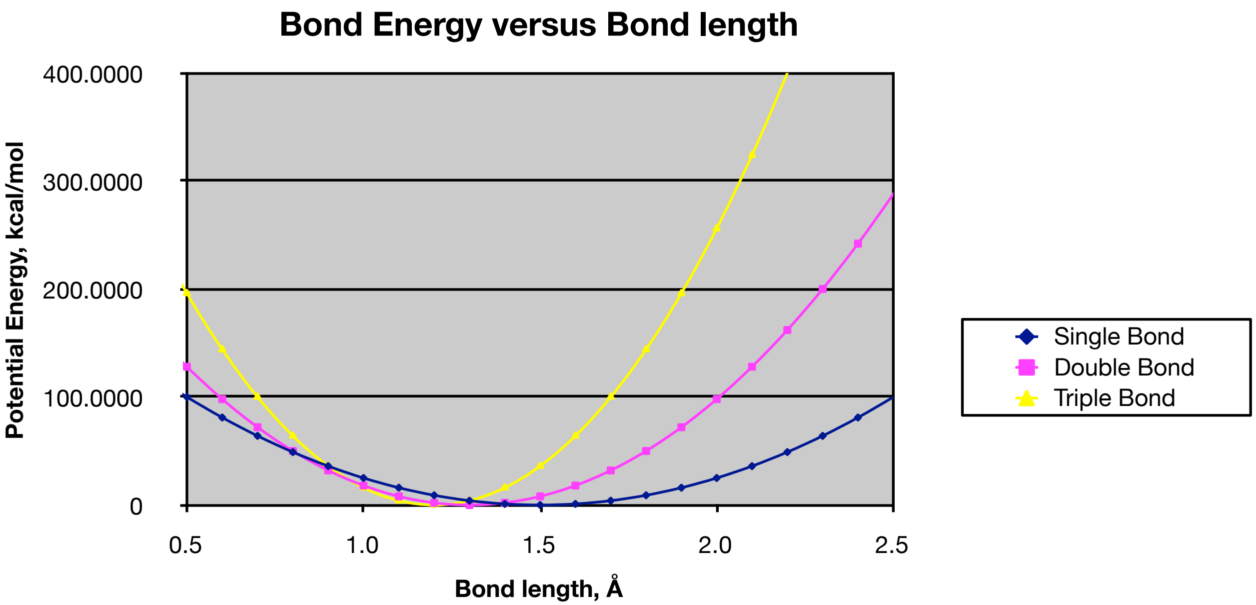


$$V_{dihedral} = K_\phi(1 + \cos(n\phi - \delta))$$

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

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

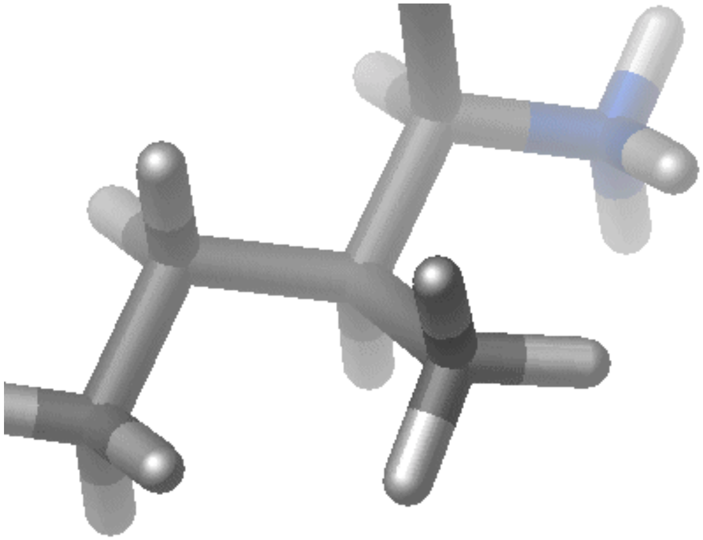


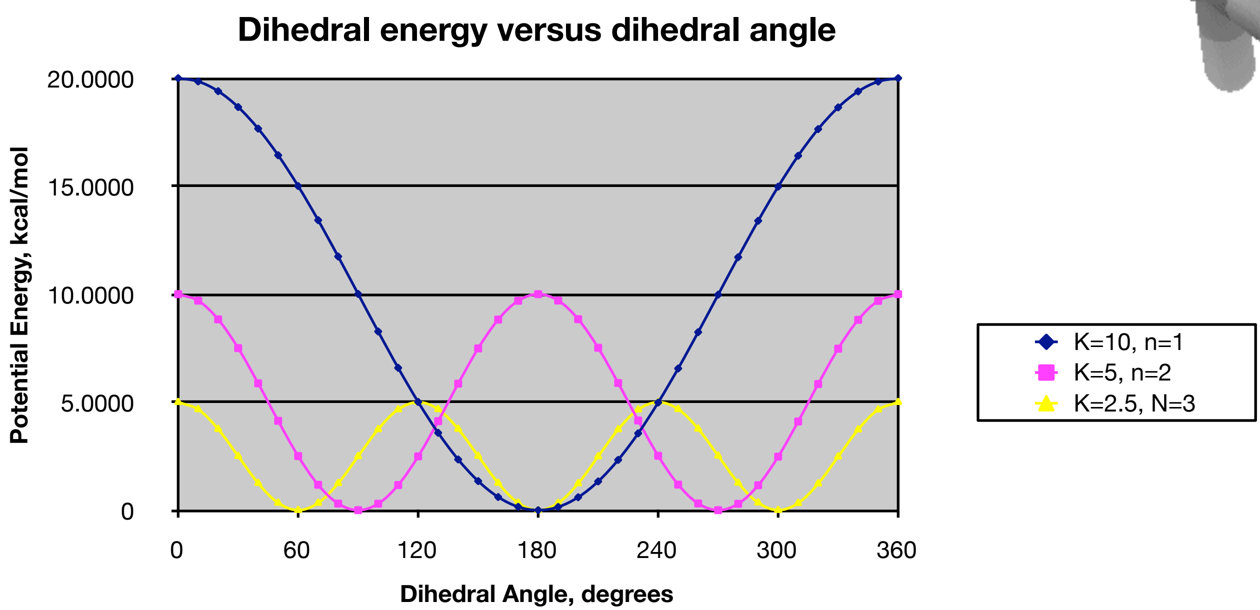


Bond angles and *improper* terms have similar quadratic forms, but with softer spring constants. The force constants can be obtained from vibrational analysis of the molecule (experimentally or theoretically).

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

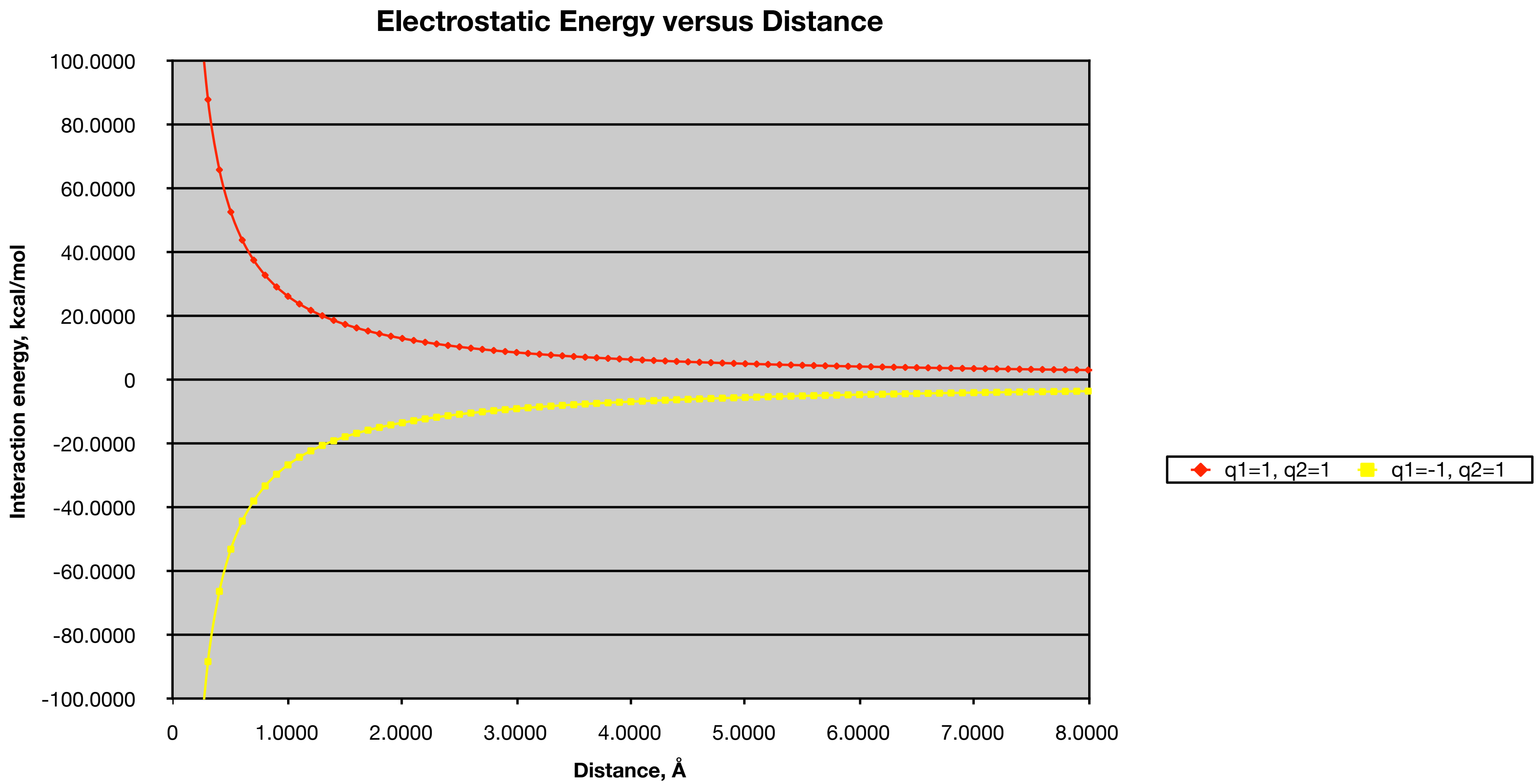
ε: Lennard-Jones (LJ, vdW) well-depth

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

Combining rules (CHARMM, Amber)

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

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



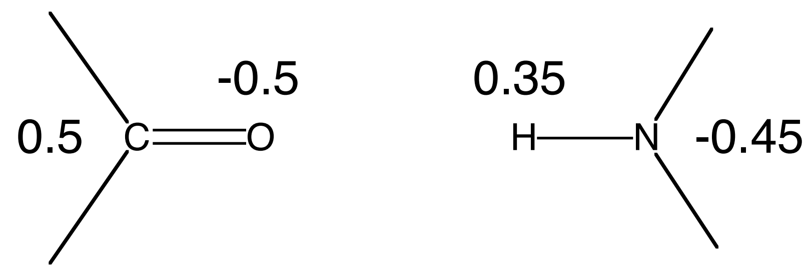
Note that the effect is long range.

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
0000000000000000000000000000000000000000000000000000000000000000000000000
        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

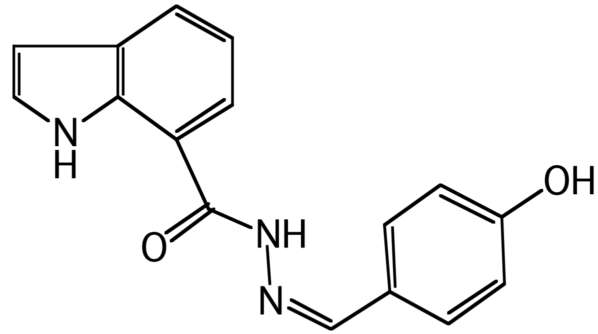
CHARMM topology (parameter files)

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)

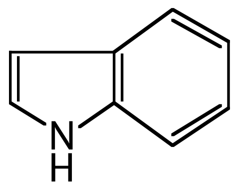
NA and lipid force fields have new LJ parameters for the alkanes, representing increased optimization of the protein alkane parameters. Tests have shown that these are compatible (e.g. in protein-nucleic acid simulations). For new systems is suggested that the new LJ parameters be used. Note that only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

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

Break Desired Compound into 3 Smaller Ones

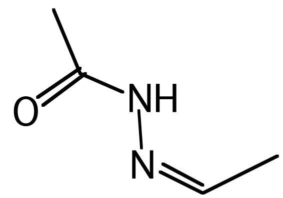


A



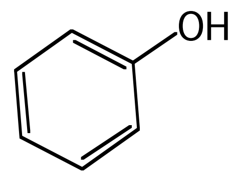
Indole

B



Hydrazine

C



Phenol

When creating a covalent link between model compounds move the charge on the deleted H into the carbon to maintain integer charge (i.e. methyl (q_C=-0.27, q_H=0.09) to methylene (q_C=-0.18, q_H=0.09)

From MacKerell

From top_all22_model.inp

```
RESI PHEN          0.00   ! phenol, adm jr.
GROUP
ATOM CG   CA    -0.115  !
ATOM HG   HP     0.115  !         HD1  HE1
GROUP                   !          |    |
ATOM CD1  CA    -0.115  !         CD1--CE1
ATOM HD1  HP     0.115  !         //     \\
GROUP                   !     HG--CG      CZ--OH
ATOM CD2  CA    -0.115  !         \       /    \
ATOM HD2  HP     0.115  !         CD2==CE2     HH
GROUP                   !          |    |
ATOM CE1  CA    -0.115  !         HD2  HE2
ATOM HE1  HP     0.115
GROUP
ATOM CE2  CA    -0.115
ATOM HE2  HP     0.115
GROUP
ATOM CZ   CA     0.110
ATOM OH   OH1   -0.540
ATOM HH   H      0.430
BOND CD2 CG CE1 CD1 CZ CE2 CG HG CD1 HD1
BOND CD2 HD2 CE1 HE1 CE2 HE2 CZ OH OH HH
DOUBLE CD1 CG CE2 CD2  CZ CE1
```

Top_all22_model.inp contains all protein model compounds. Lipid, nucleic acid and carbohydate model compounds are in the full topology files.

HG will ultimately be deleted. Therefore, move HG (hydrogen) charge into CG, such that the CG charge becomes 0.00 in the final compound.

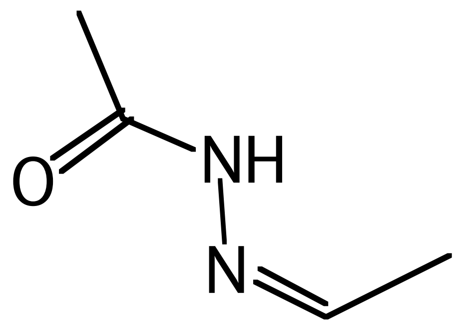
Use remaining charges/atom types without any changes.

Do the same with indole

From MacKerell

Creation of topology for central model compound

```
RESI  Mod1 ! Model compound 1
Group
ATOM C1   CT3   -0.27
ATOM H11  HA3    0.09
ATOM H12  HA3    0.09
ATOM H13  HA3    0.09
GROUP
ATOM C2   C      0.51
ATOM O2   O     -0.51
GROUP
ATOM N3   NH1   -0.47
ATOM H3   H      0.31
ATOM N4   NR1    0.16   !new atom
ATOM C5   CEL1  -0.15
ATOM H51  HEL1   0.15
ATOM C6   CT3   -0.27
ATOM H61  HA     0.09
ATOM H62  HA     0.09
ATOM H63  HA     0.09
BOND C1 H11 C1 H12 C1 H13 C1 C2 C2 O2 C2 N3 N3 H3
BOND N3 N4 C5 H51 C5 C6 C6 H61 C6 H62 C6 H63
DOUBLE N4 C5 (DOUBLE only required for MMFF)
```



Start with alanine dipeptide. Note use of new aliphatic LJ parameters and, importantly, atom types.

NR1 from histidine unprotonated ring nitrogen. Charge (very bad) initially set to yield unit charge for the group.

Note use of large group to allow flexibility in charge optimization.

From MacKerell

Partial Charge Assignment

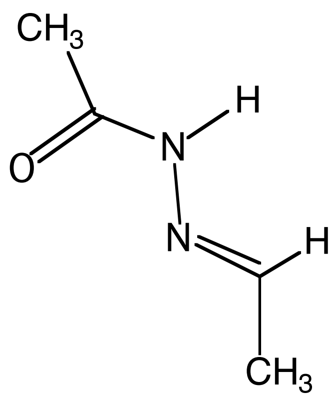
- Most important aspect for ligands

- 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



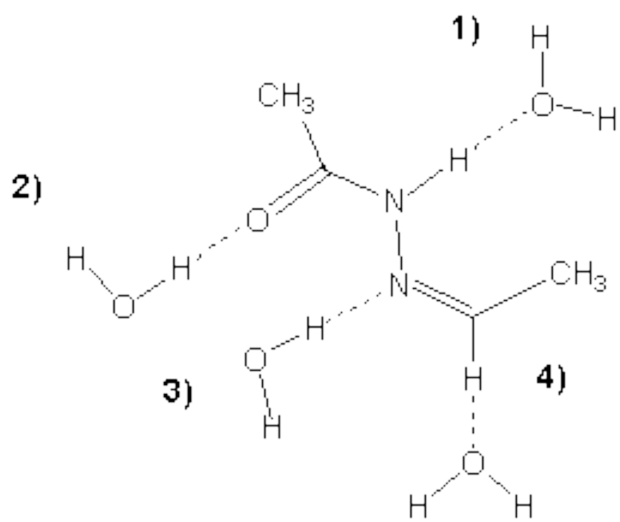
Starting charges??

Mulliken population analysis

Analogy comparison

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

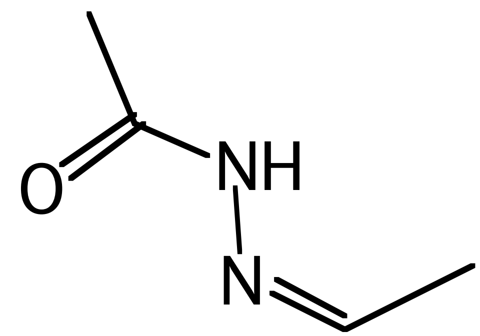
interactions with water (HF/6-31G*, monohydrates!)



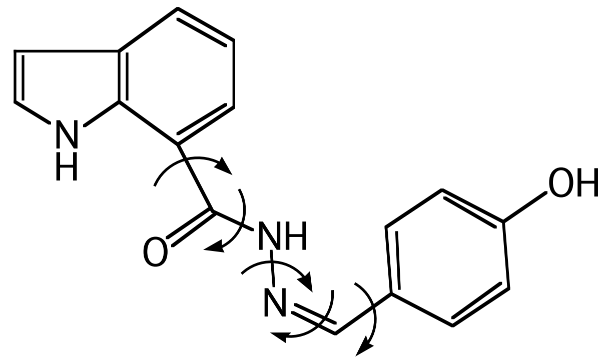
From MacKerell

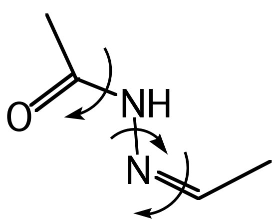
Comparison of analogy and optimized charges

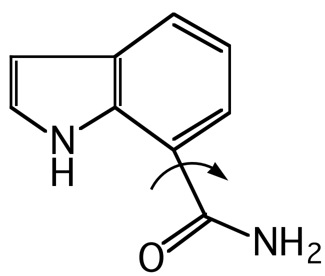
Name	Type	Analogy	Optimized
C1	CT3	-0.27	-0.27
H11	HA3	0.09	0.09
H12	HA3	0.09	0.09
H13	HA3	0.09	0.09
C2	C	0.51	0.58
O2	O	-0.51	-0.50
N3	NH1	-0.47	-0.32
H3	H	0.31	0.33
N4	NR1	0.16	-0.31
C5	CEL1	-0.15	-0.25
H51	HEL1	0.15	0.29
C6	CT3	-0.27	-0.09
H61	HA	0.09	0.09
H62	HA	0.09	0.09
H63	HA	0.09	0.09

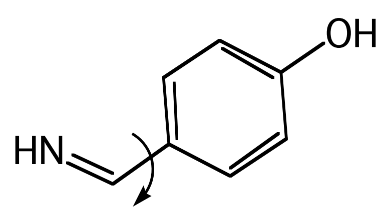


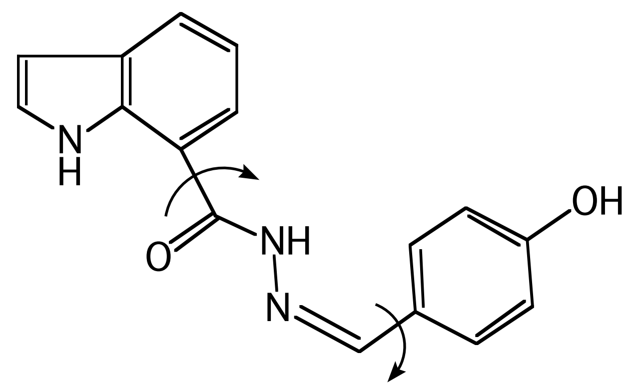
Dihedral optimization based on QM potential energy surfaces (HF/6-31G* or MP2/6-31G*).







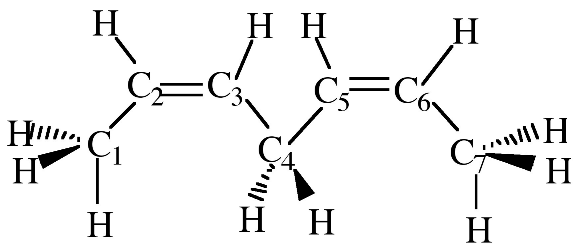


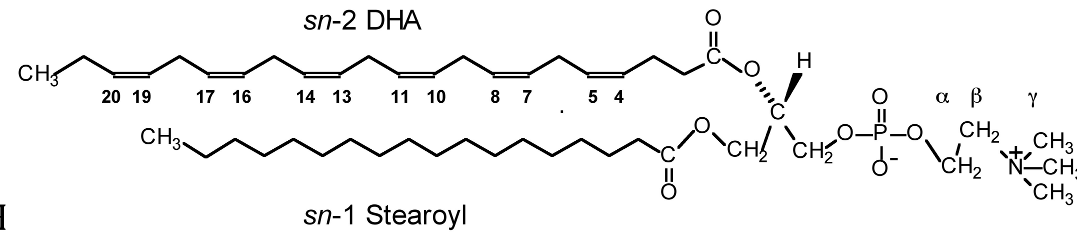


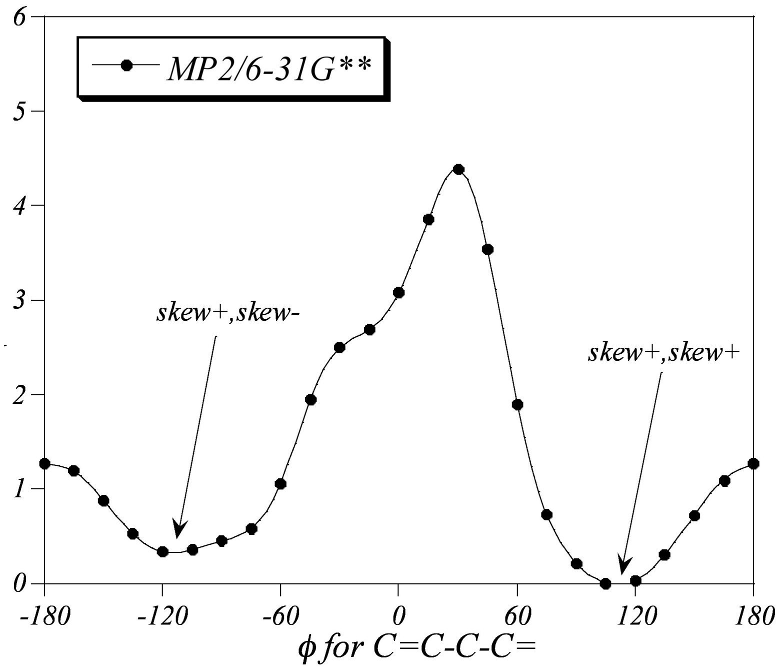
From MacKerell

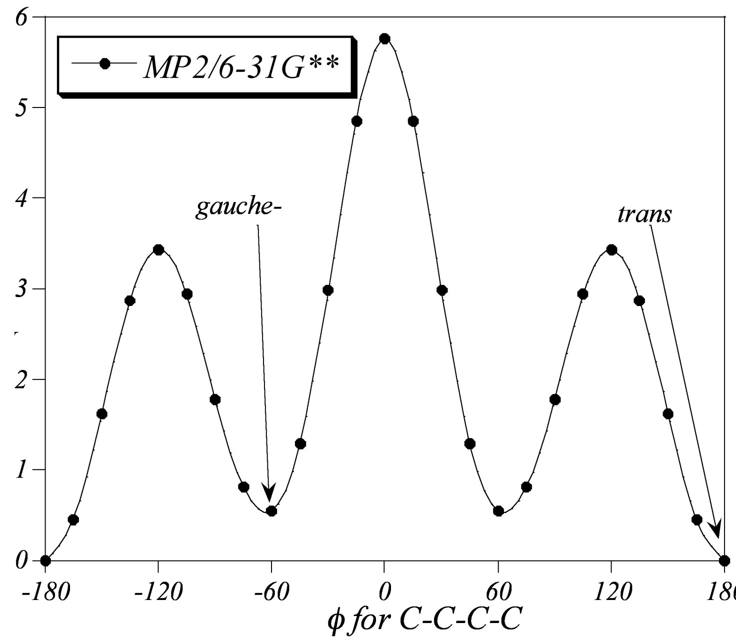
Parameterization of unsaturated lipids

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





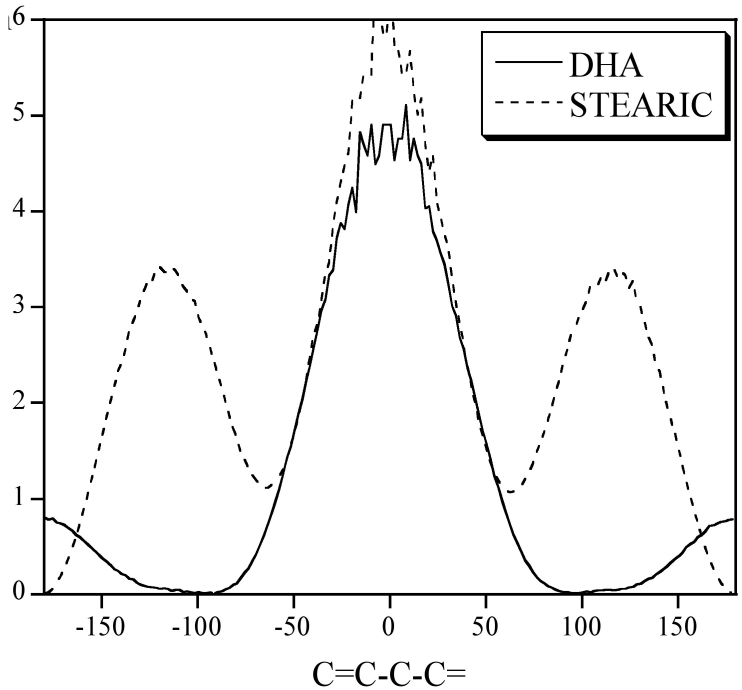


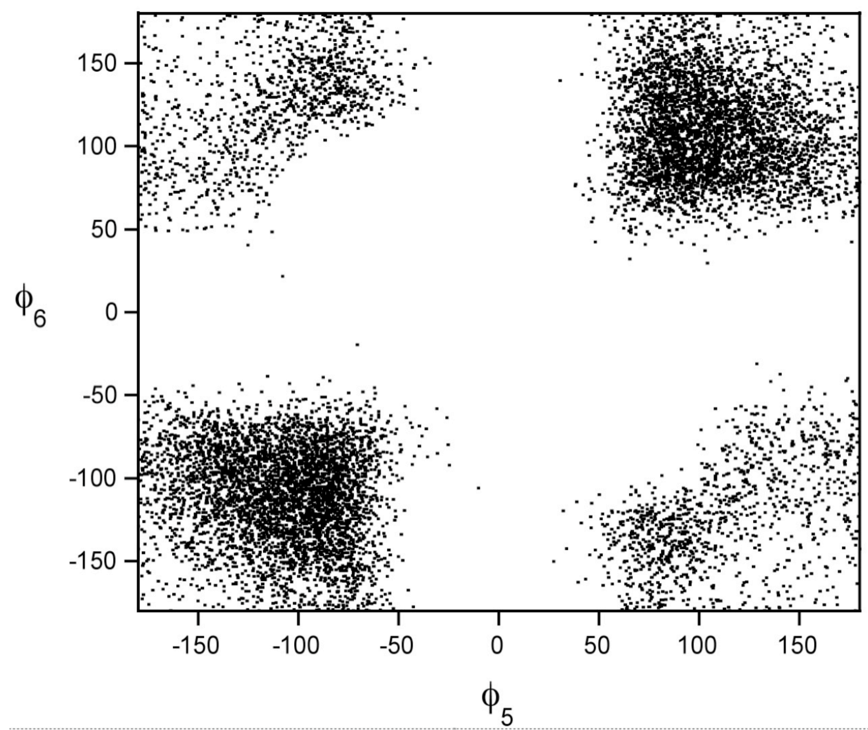


Courtesy of Scott Feller, Wabash College

DHA conformations from MD

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

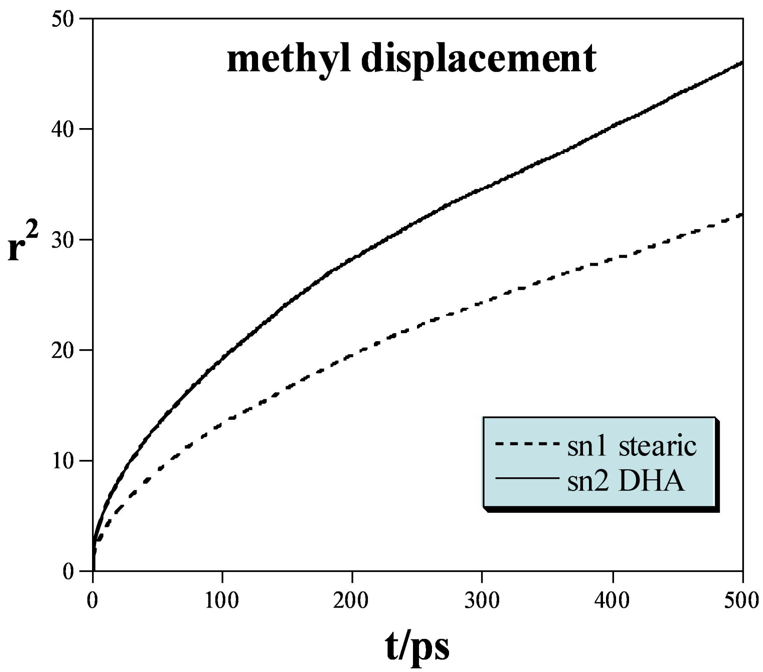


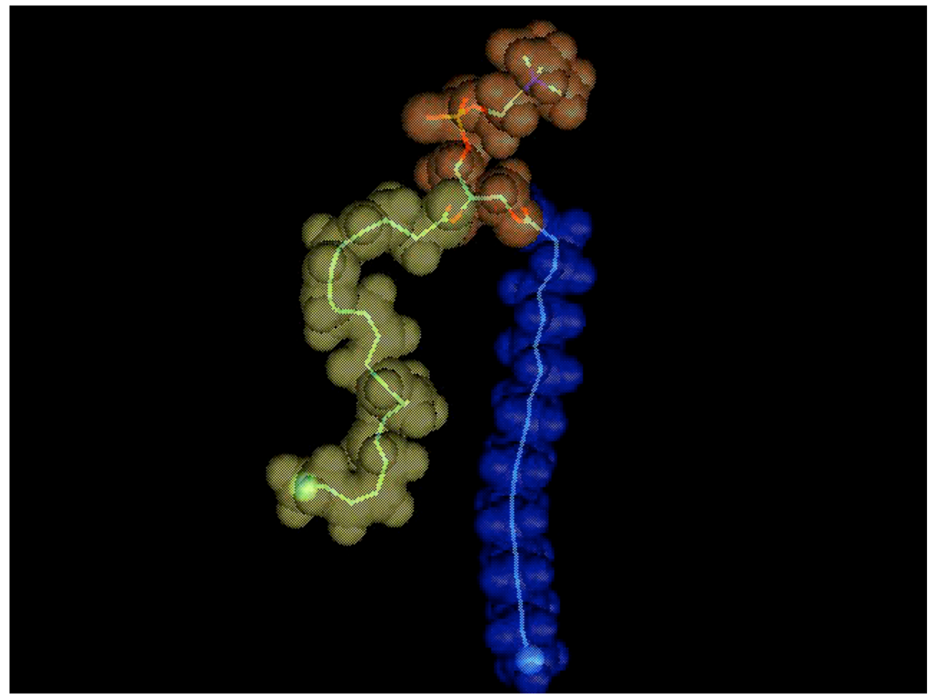


Courtesy of Scott Feller, Wabash College

Dynamics of saturated vs. polyunsaturated lipid chains

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



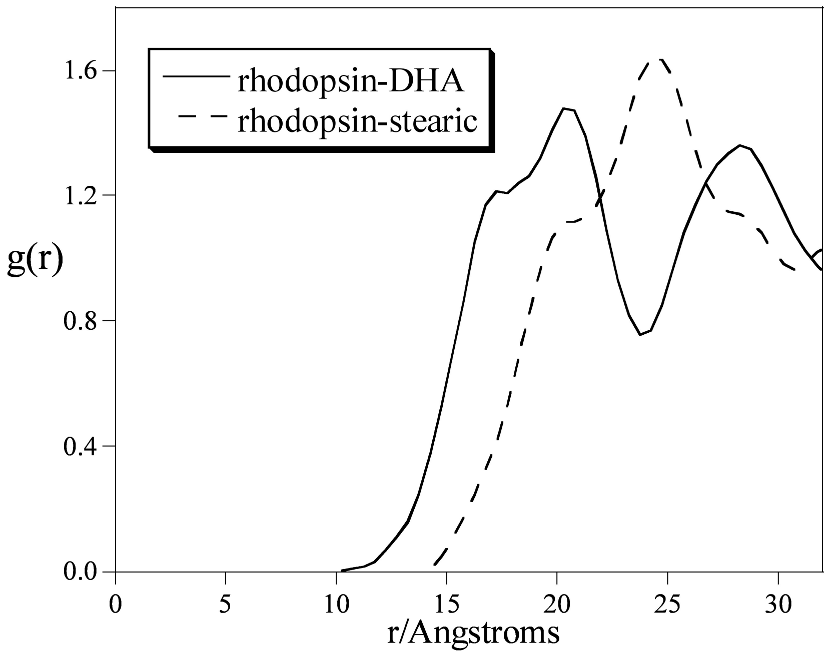


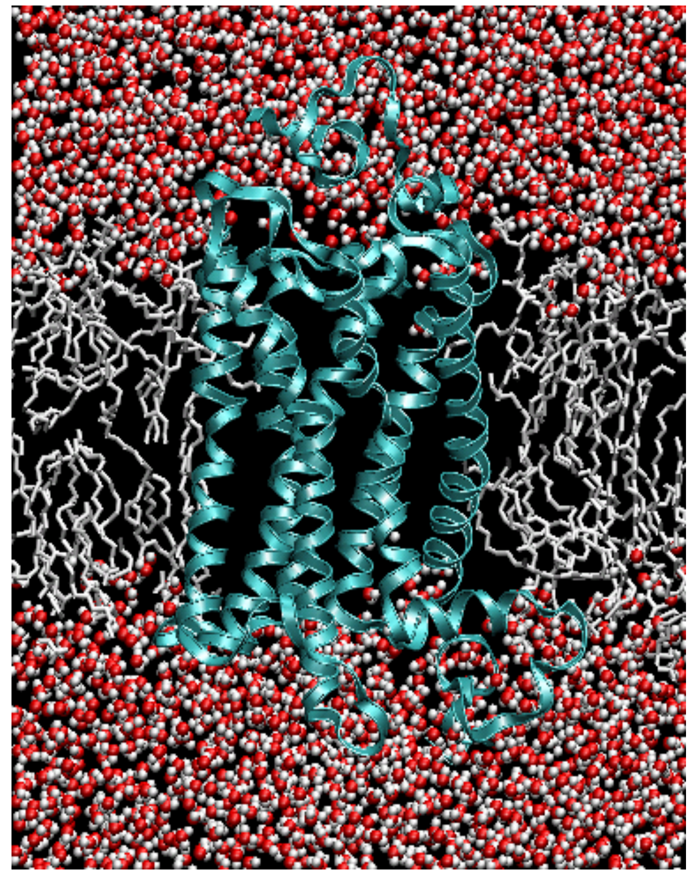
Movie courtesy of Mauricio Carrillo Tripp

Courtesy of Scott Feller, Wabash College

Lipid-protein interactions

- Radial distribution around protein shows distinct layering of acyl chains

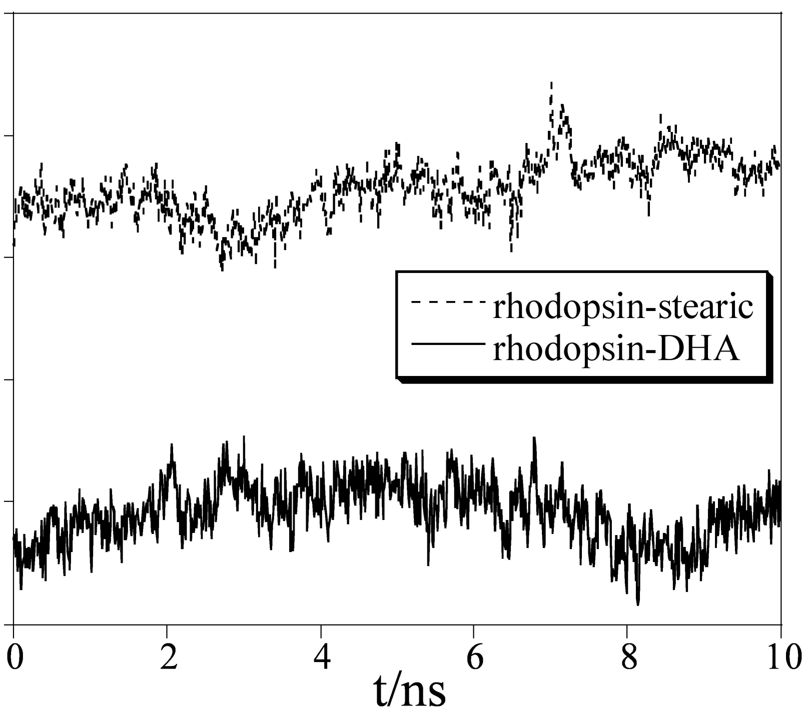




Courtesy of Scott Feller, Wabash College

Lipid-protein interactions

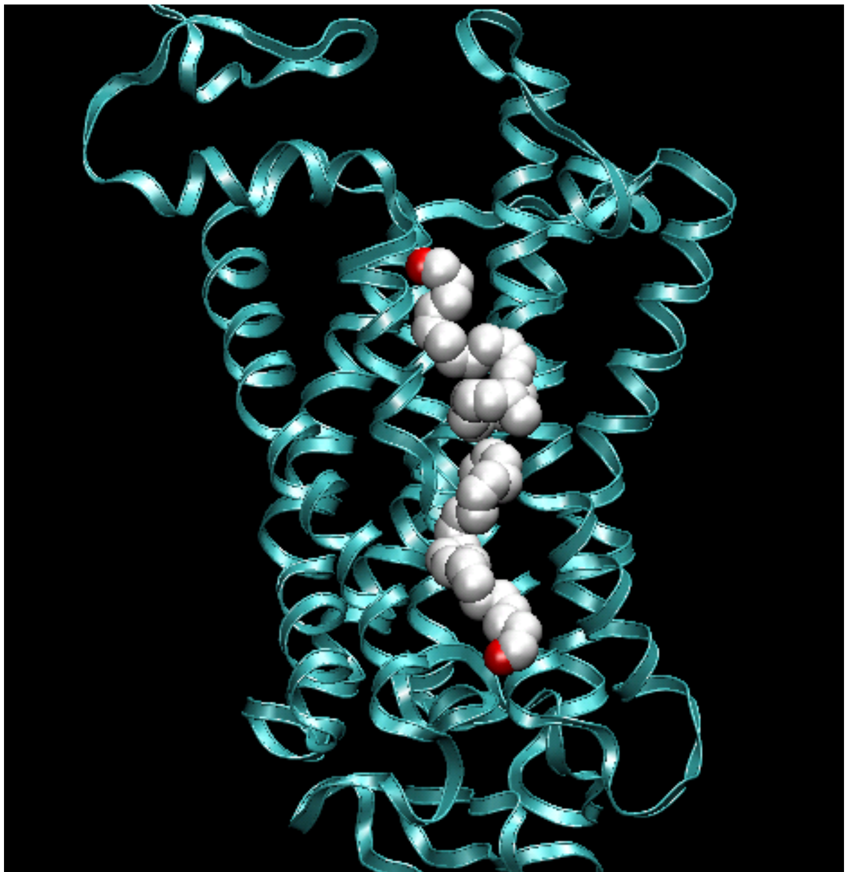
- Decomposition of non-bonded interaction shows rhodopsin is strongly attracted to unsaturated chain
- All hydrophobic residues are stabilized by DHA

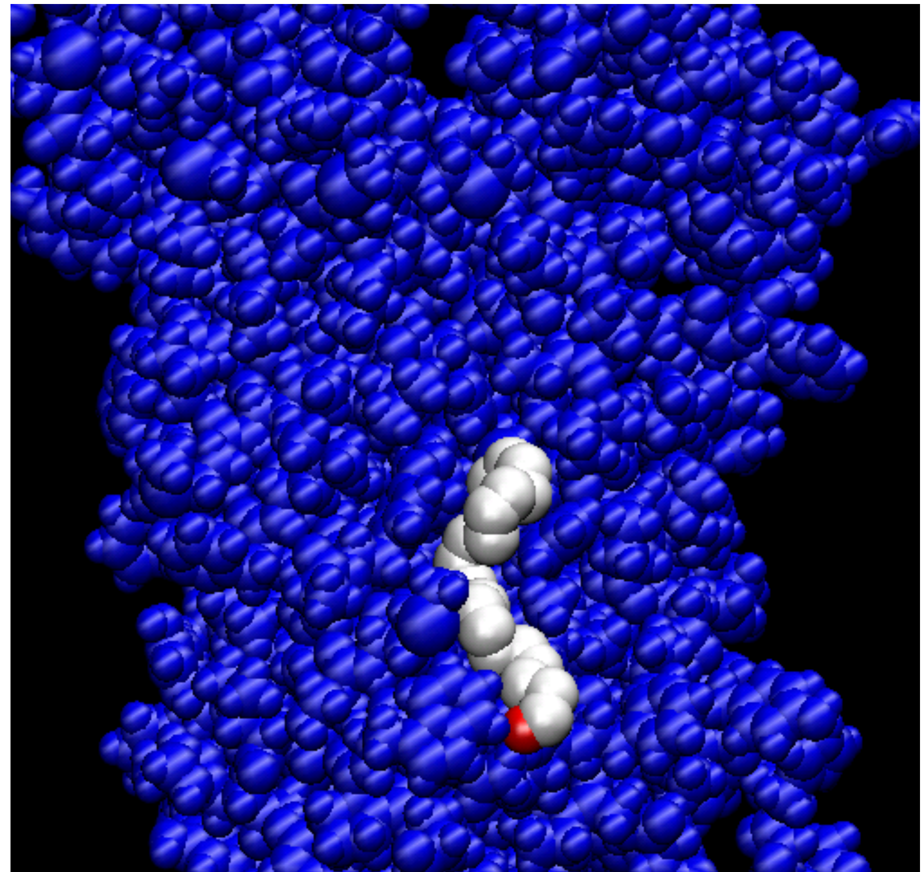


resname	U_{DHA}	$U_{stearic}$	ratio
PHE	-44.9	-22.6	2.0
ILE	-30.0	-10.1	3.0
VAL	-24.0	-9.6	2.5
LEU	-23.1	-13.0	1.8
MET	-22.8	-9.7	2.4
TYR	-18.6	-10.4	1.8
ALA	-11.4	-3.0	3.8
TRP	-10.3	-2.4	4.2

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

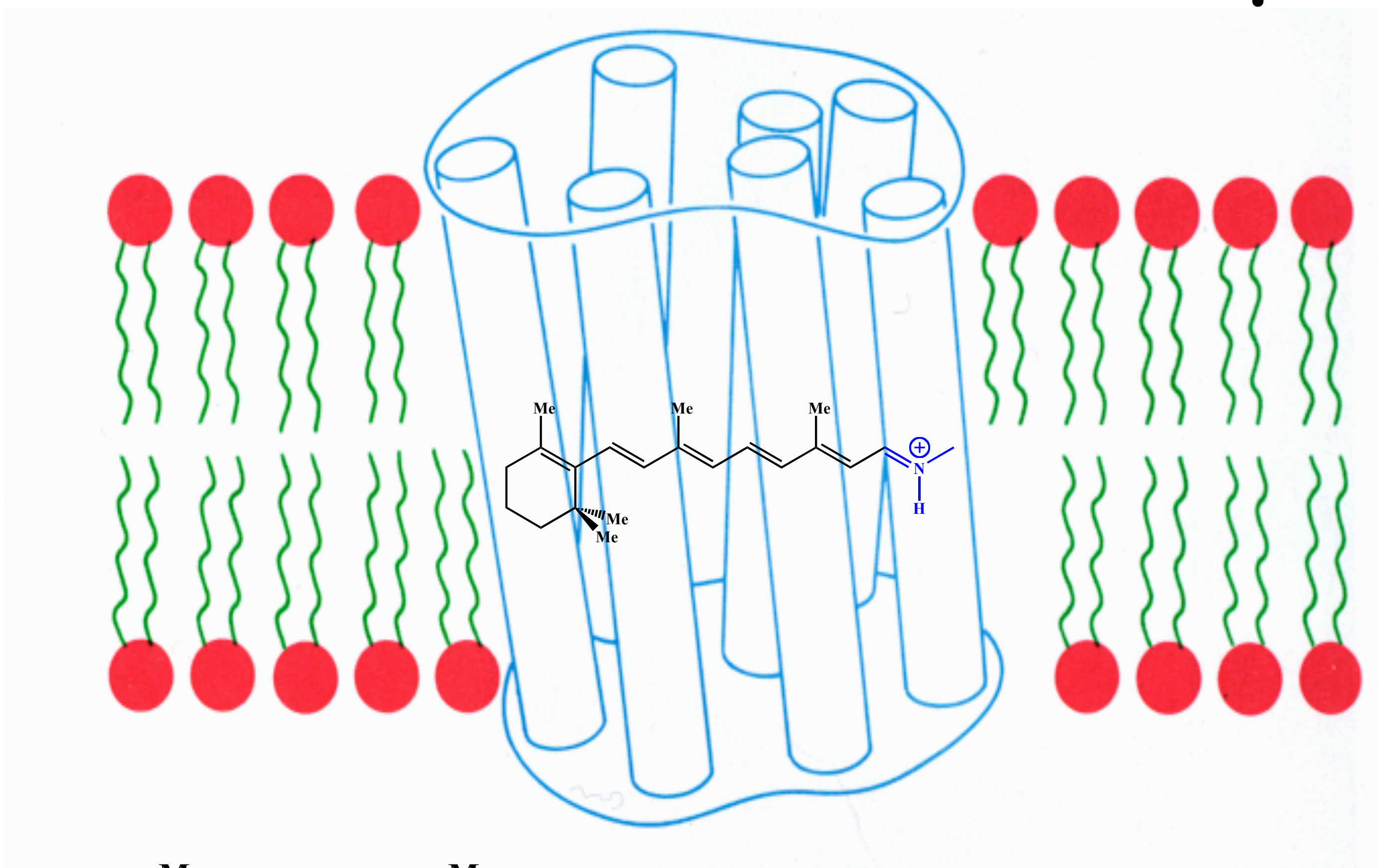
Courtesy of Scott Feller, Wabash College

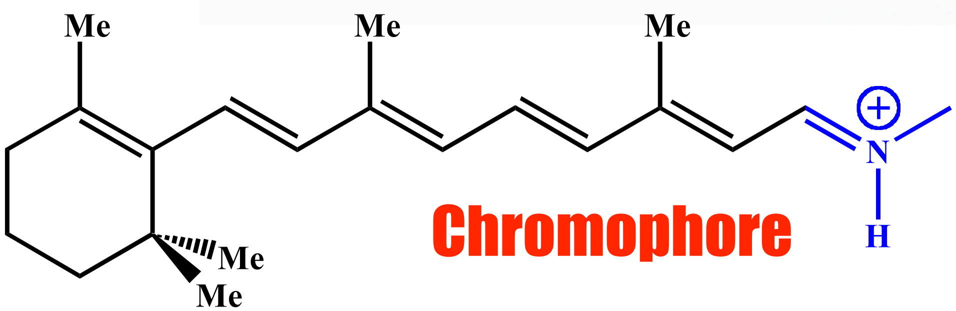
Major Recent Developments

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

- Polarizable force field
  - Roux, MacKerell

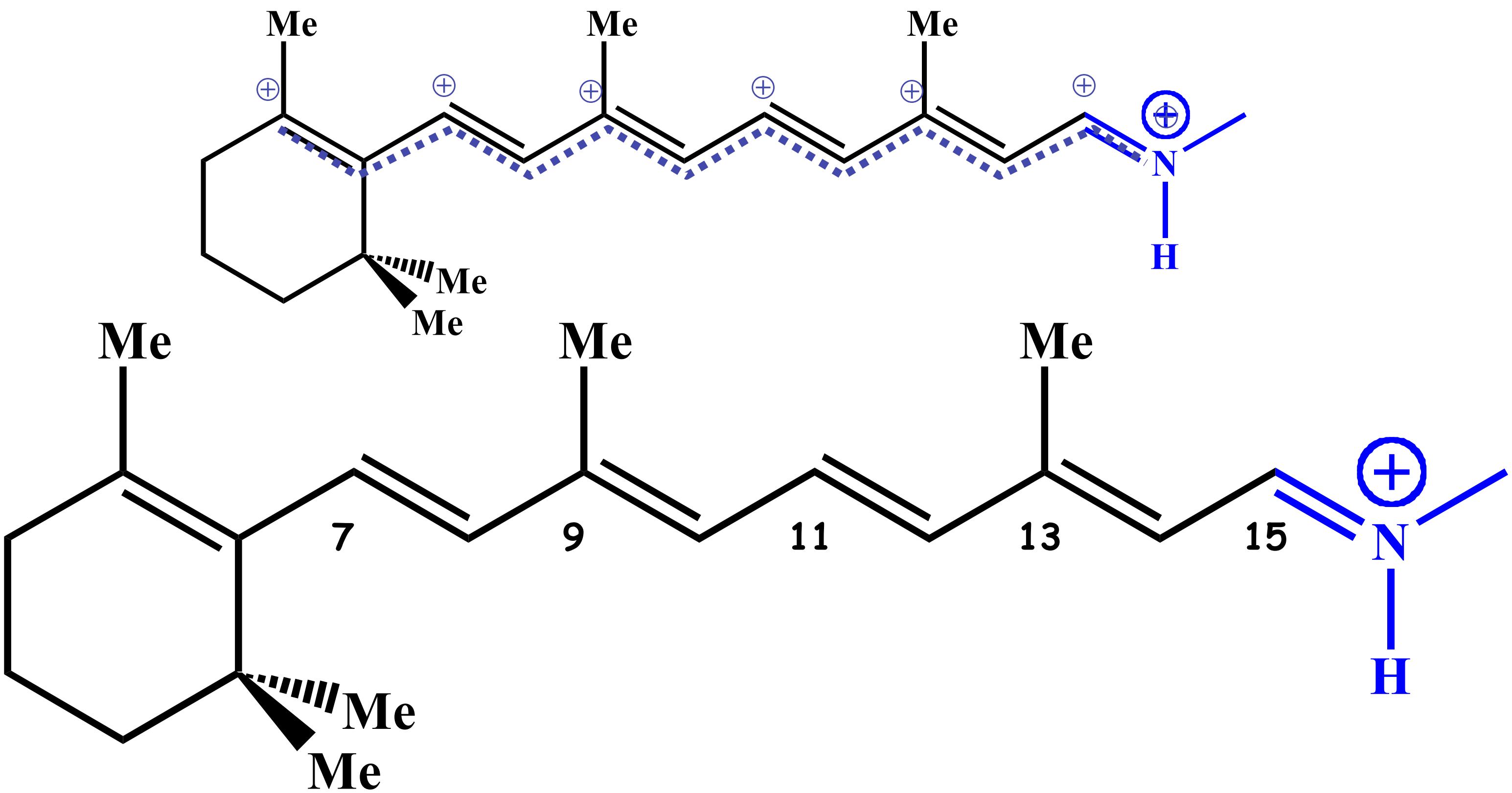
Retinal Proteins -- Rhodopsins



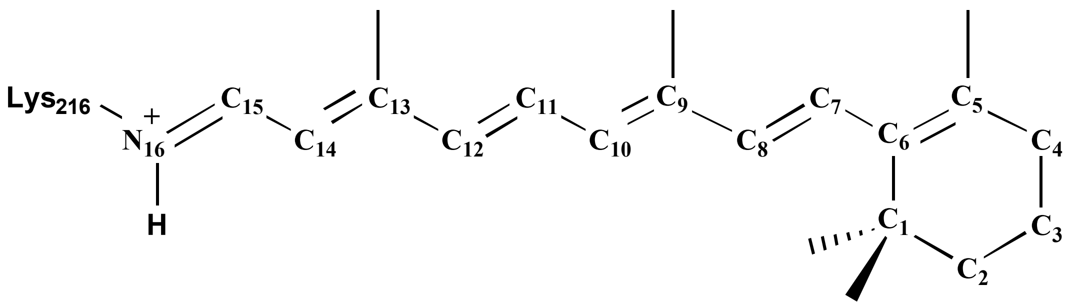


- Covalently linked to a lysine
- Usually protonated Schiff base
- all-trans and 11-cis isomers

Unconventional chemistry



Isomerization Barriers in retinal



DFT/6-31G**

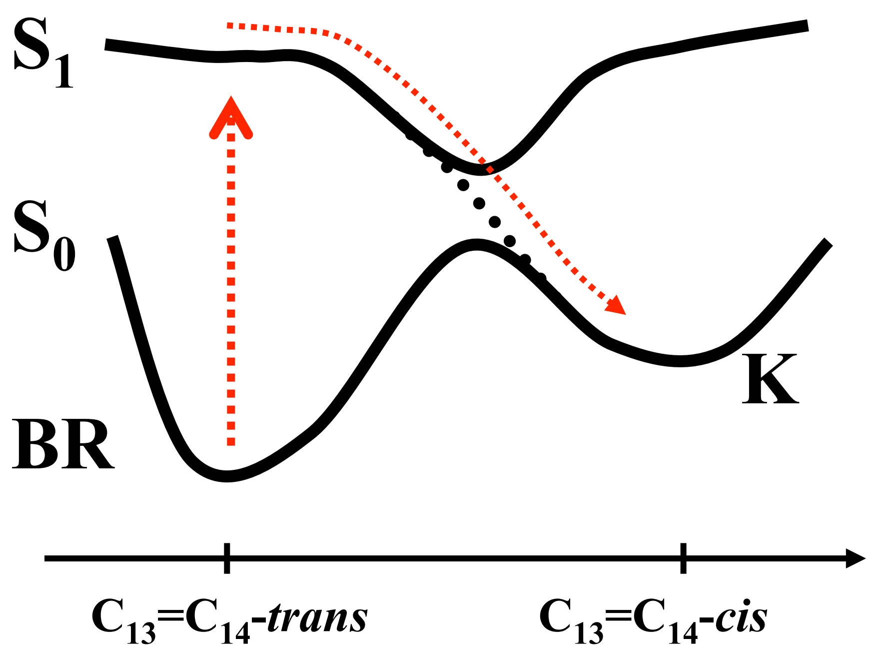
TABLE 2 The parameter set B used for the torsional potentials of the main polyene chain of the retinal Schiff base

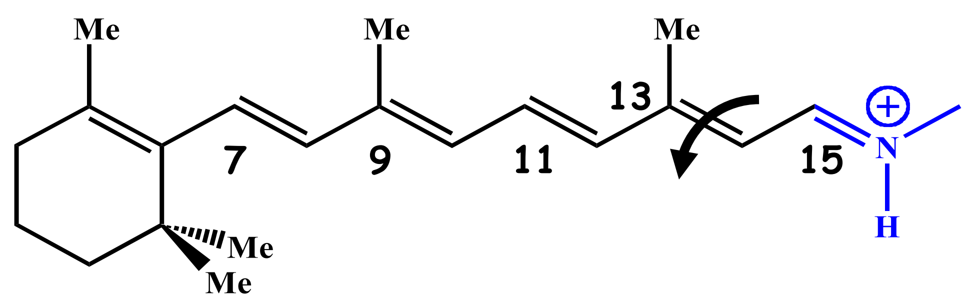
ϕ_i	k_i (kcal/mol)*	n_i	δ_i (deg)
$C_5{=}C_6{-}C_7{=}C_8$	11.24	2.0	180.00
$C_6{-}C_7{=}C_8{-}C_9$	39.98	2.0	180.00
$C_7{=}C_8{-}C_9{=}C_{10}$	17.03	2.0	180.00
$C_8{-}C_9{=}C_{10}{-}C_{11}$	37.28	2.0	180.00
$C_9{=}C_{10}{-}C_{11}{=}C_{12}$	22.50	2.0	180.00
$C_{10}{-}C_{11}{=}C_{12}{-}C_{13}$	35.08	2.0	180.00
$C_{11}{=}C_{12}{-}C_{13}{=}C_{14}$	28.30	2.0	180.00
$C_{12}{-}C_{13}{=}C_{14}{-}C_{15}$	29.46	2.0	180.00
$C_{13}{=}C_{14}{-}C_{15}{=}N_{16}$	30.43	2.0	180.00
$C_{14}{-}C_{15}{=}N_{16}{-}C_{\varepsilon}$	28.76	2.0	180.00

Tajkhorshid et al., 1999.

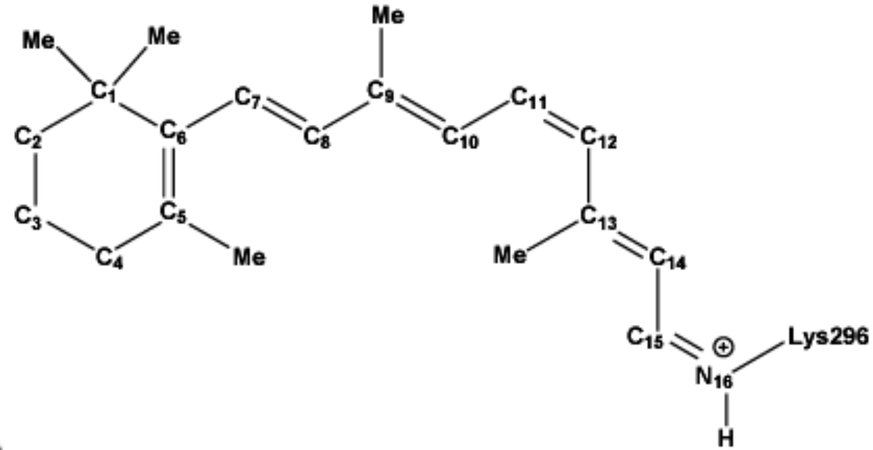
$*E_i^{\mathrm{dihedral}} = (1/2)k_i[1 + \cos(n_i\varphi_i - \delta_i)]$.

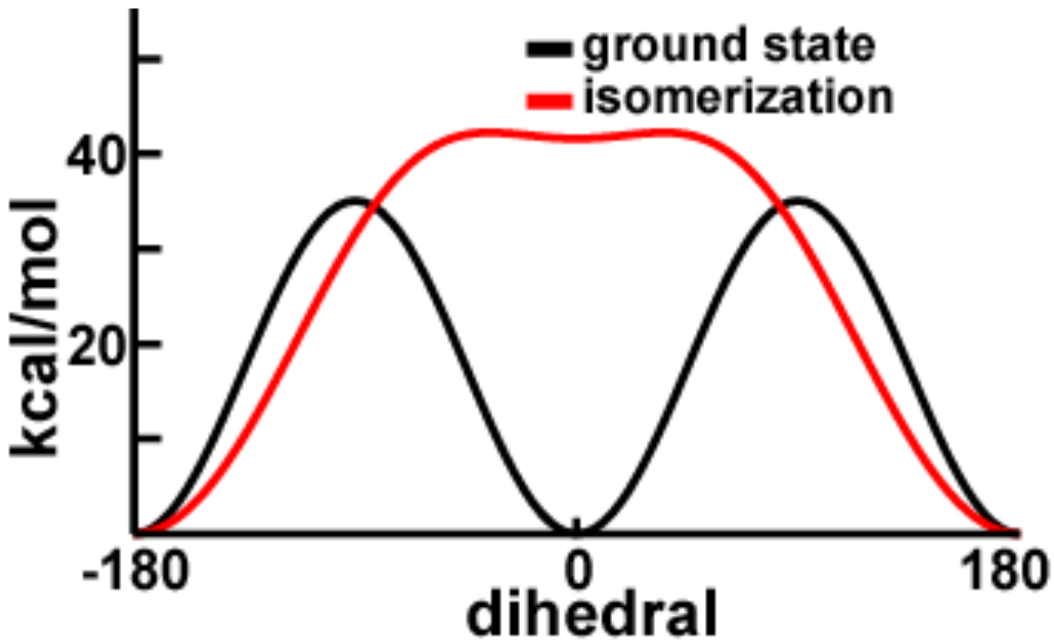
Coupling of electronic excitation and conformational change in bR





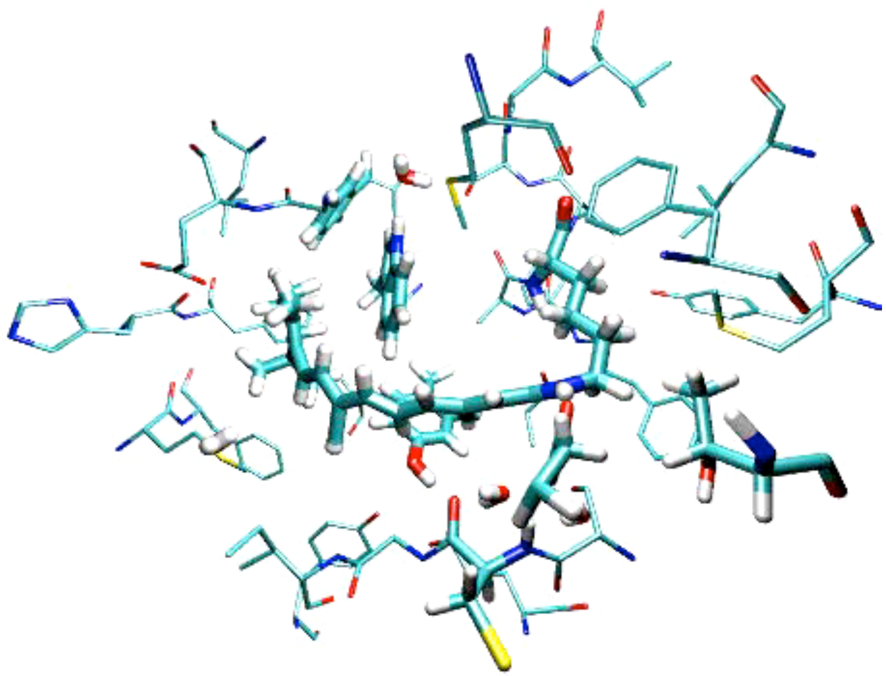
Inducing isomerization

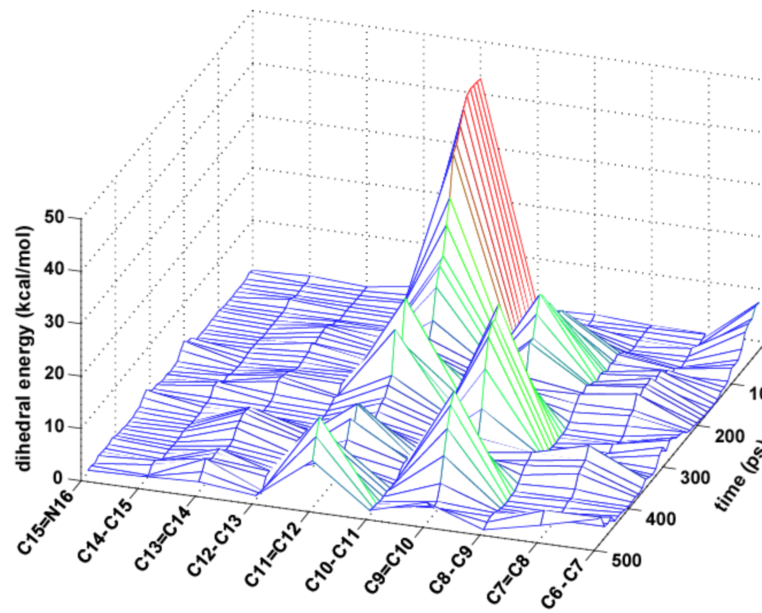




500 nm
~50 kcal/mole

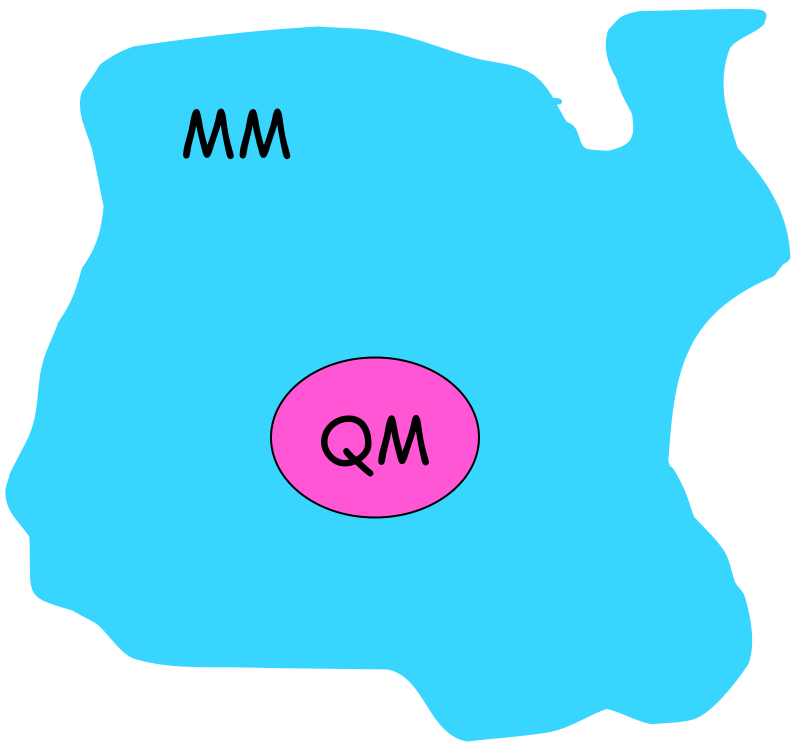
Classical Retinal Isomerization

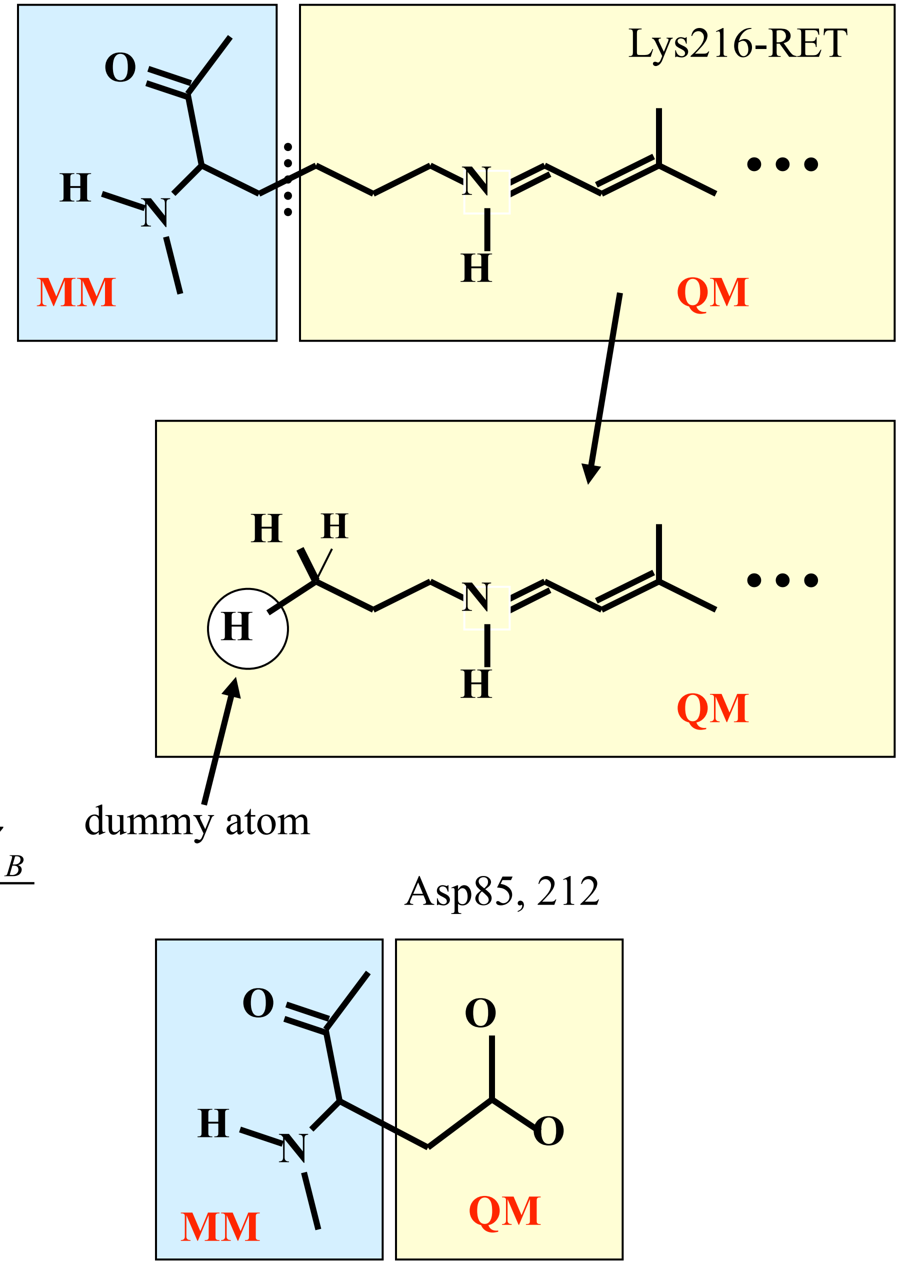




Twist Propagation

QM/MM calculations



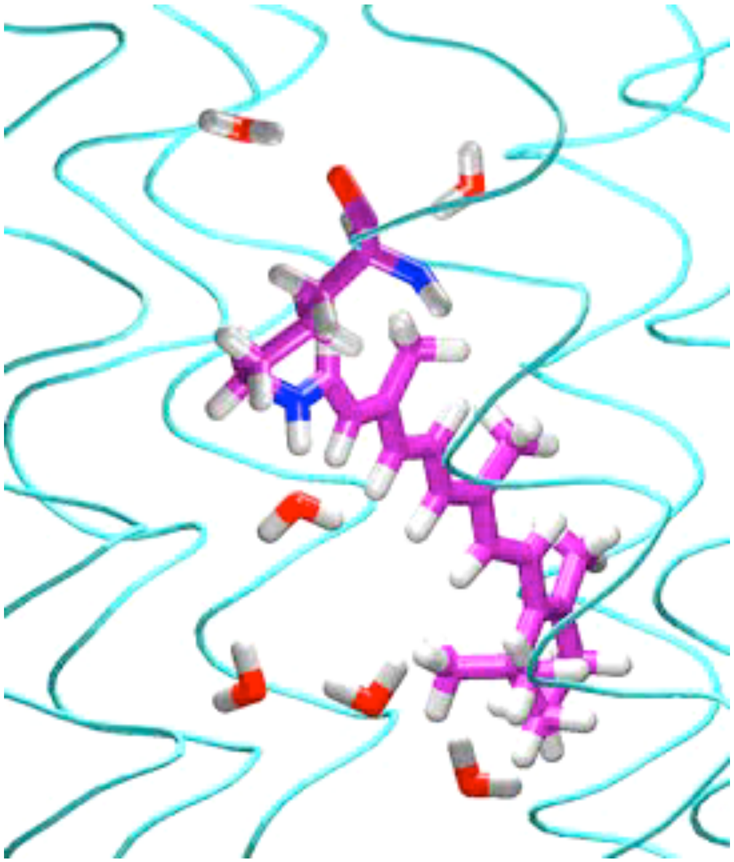


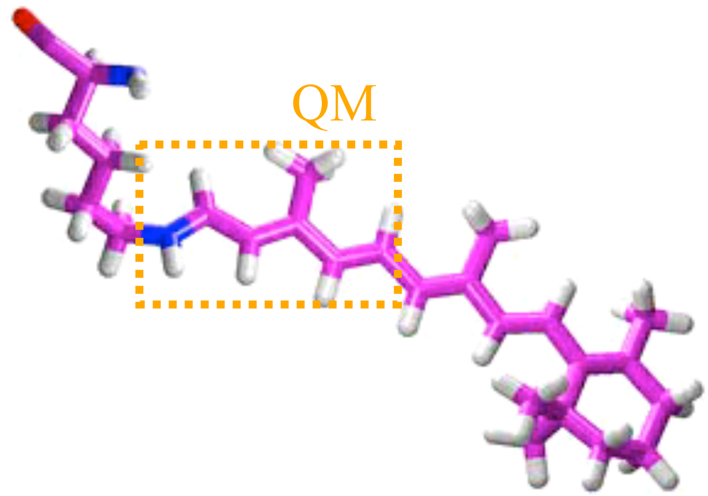
$$\hat{H} = \sum_i \frac{1}{2} p_i^2 + \sum_i \sum_A \frac{Z_A}{r_{iA}} + \sum_{i>j} \frac{1}{r_{ij}} + \sum_{A>B} \frac{Z_A Z_B}{r_{AB}}$$

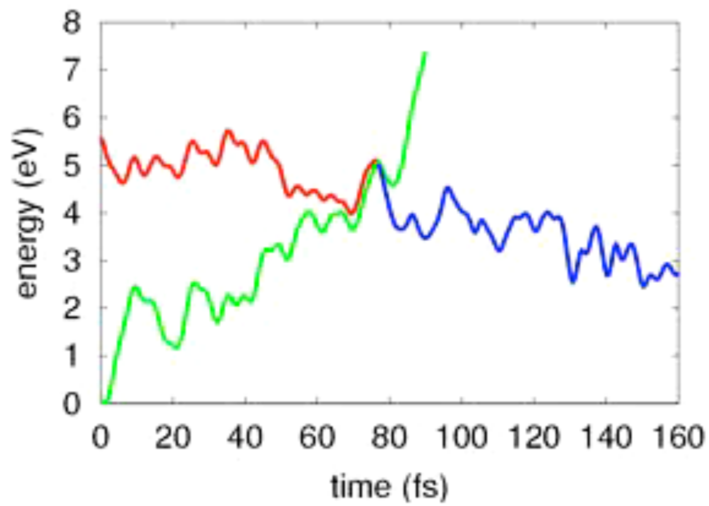
$$+ \sum_i \sum_p \frac{q_p}{r_{ip}} + \sum_A \sum_p \frac{Z_A q_p}{r_{Ap}}$$

$$+ V_{QM-MM}^{MM} + V_{MM}^{MM}$$

Ab Initio QM/MM Excited State MD Simulation

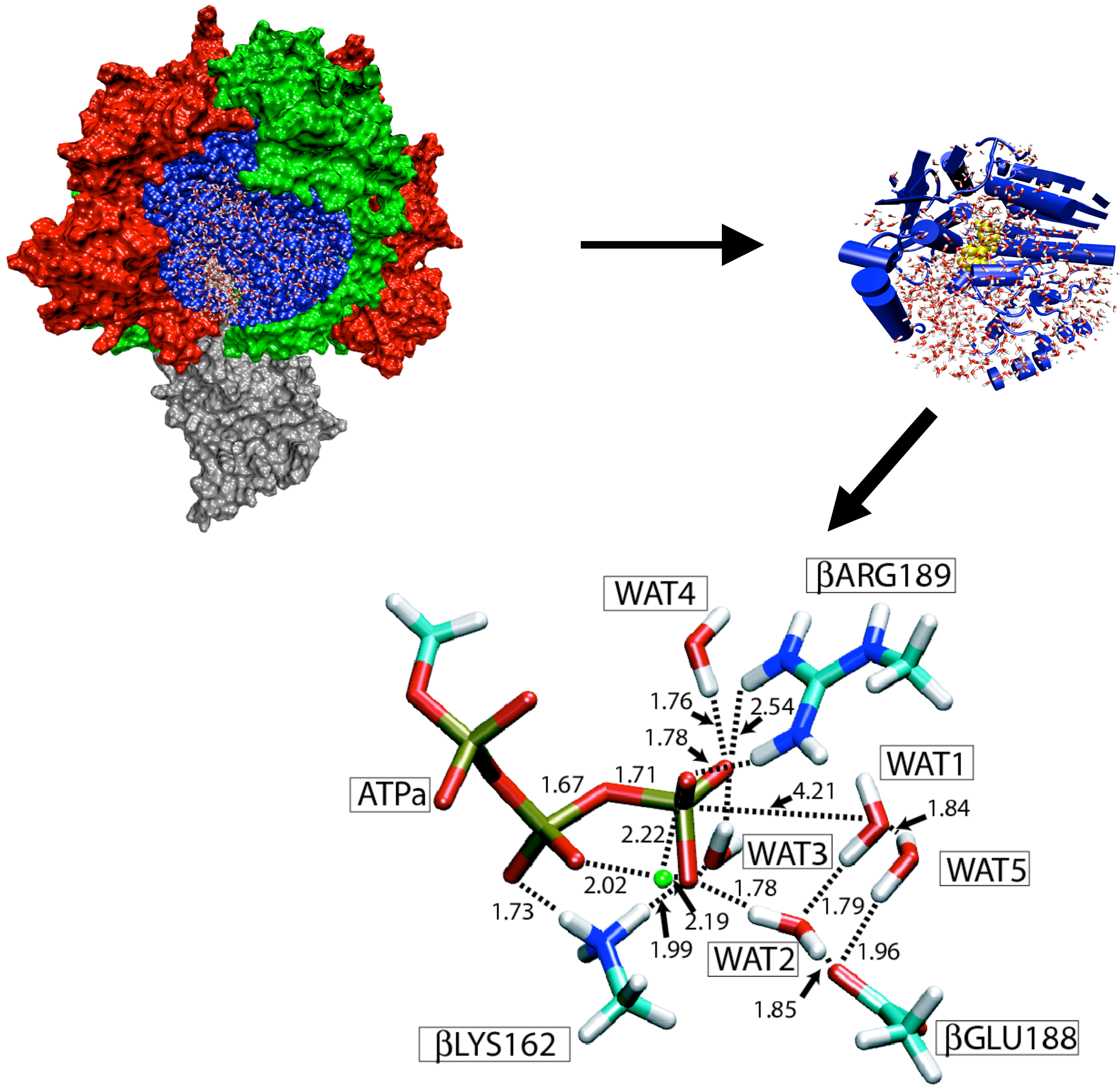






Quantum mechanical (QM) treatment of the chromophore, and force field (MM) treatment of the embedding protein

QM/MM calculation of ATP hydrolysis



Coarse grain modeling of lipids

150 particles

9 particles!

(A)