

Hybrid Quantum – Classical Simulations:

An Introduction to the QM / MM Method

Lecture 2:

Molecular Mechanics: Empirical Force Fields

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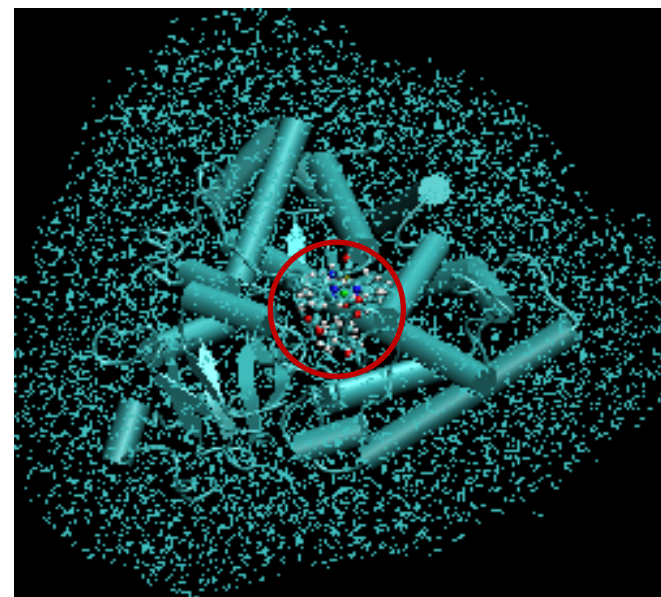
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Molecular Mechanics : Empirical Force Fields

- Many of the problems that we would like to deal with are unfortunately too large to be considered by quantum mechanical methods.

Number of atoms – 1000 or 100,000 or more.

- Force field methods (MM) ignore the electronic motions and calculate the energy of a system as a function of the nuclear coordinates only.
- MM is suitable for performing calculations on systems with large number of molecules. Models contain parameters which can be tuned to improve accuracy.
- MM, of course, cannot provide properties that depend upon the electronic distributions (chemical reactions, electronic excitations, charge transfers etc.)

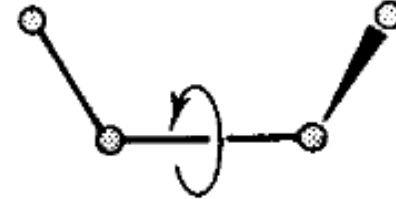
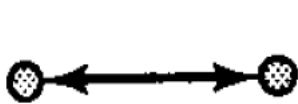


Simple molecular mechanics force fields

- Many of the molecular force fields in use today can be interpreted in terms of a relatively simple five-component picture of the intra and inter-molecular interactions.

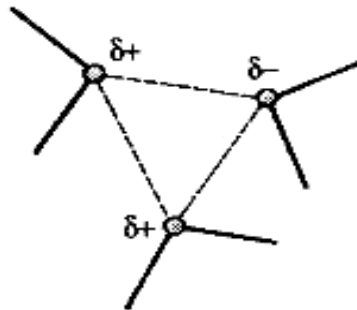
$$V(r^N) =$$

Bond stretching + Bond bending + Bond rotation (torsion)

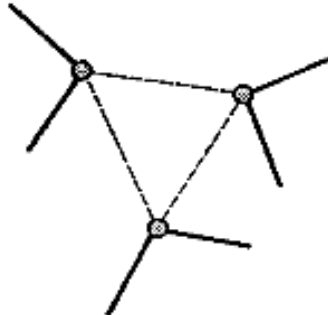


+ Non-bonded interactions

Electrostatic



van der Waals



Ref. A. R. Leach, *Molecular Modelling*, Addison Wesley Longman (1998)

Bond Stretching

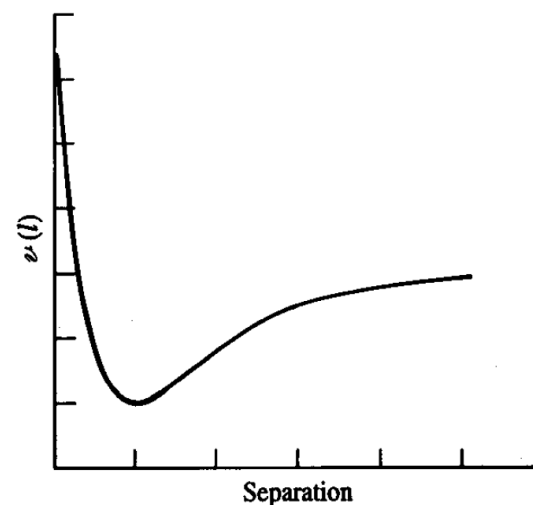
The potential energy curve for a typical bond can be described well by Morse potential

$$v(l) = D_e \left\{ 1 - e^{-a(l-l_0)} \right\}^2$$

where, D_e is well-depth and l_0 is the equilibrium bond length. Morse potential describe a wide range of behavior from equilibrium to dissociation. However, it is rare in molecular mechanics calculations for bonds to deviate significantly from their equilibrium values. Consequently, simpler expressions like Hooke's law formula is most often used

$$v(l) = \frac{1}{2} k (l - l_0)^2$$

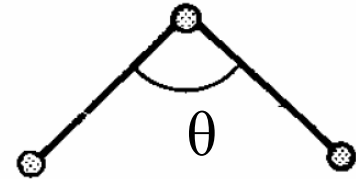
which makes a reasonably good description of bond vibration at the lower part of potential well.



Bond Bending

- The deviations of angles from their equilibrium values are also frequently described using a Hooke's law or harmonic potential

$$v(\theta) = \frac{1}{2}k(\theta - \theta_0)^2$$



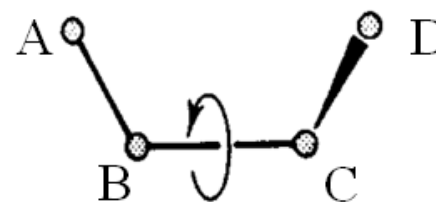
- The contribution of each angle is characterized by a force constant and an equilibrium value. Usually, force constant for bending is smaller than that of stretching.
- The bond stretching and angle bending terms are often regarded as 'hard' degrees of freedom because quite substantial energies are required to cause significant deviations from this equilibrium values. Hence, they are not considered at all in many models.

Torsion

- Most of the variation in structure and relative energies is due to the complex interplay between the torsional and non-bonded interactions.
- The existence of barriers to rotation about chemical bonds is fundamental to understand the structural properties of molecular and conformational analysis.
- Torsional contribution is included for each bonded quartet of atoms A-B-C-D in the system. Torsional potentials are usually expressed as cosine functions

$$v(\phi) = \sum_{n=0}^N \frac{V_n}{2} [1 + \cos(n\phi - \gamma)]$$

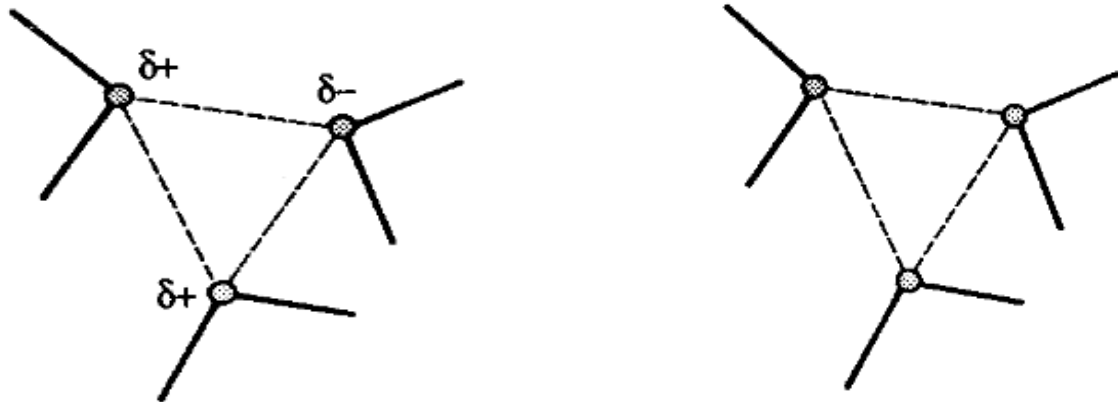
where ϕ is the torsional angle and V_n measures barrier height.



Ref. A. R. Leach, *Molecular Modelling*, Addison Wesley Longman (1998)

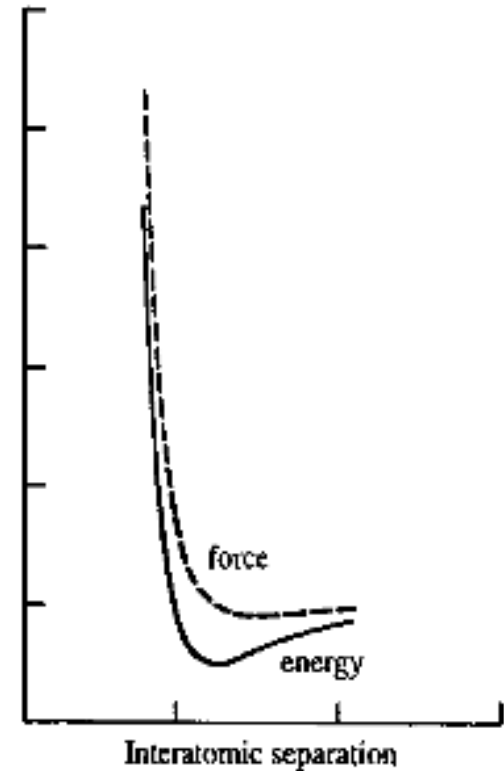
Non-bonded interaction

- The non-bonded interactions do not depend upon a specific bonding relationship between atoms . They are '*through-space*' interactions and are usually modelled as a function of some inverse power of the distance The non-bonded terms in a force field are usually considered in two groups:
 - Electrostatic interaction (long range) and
 - van der Waals interactions (short range)



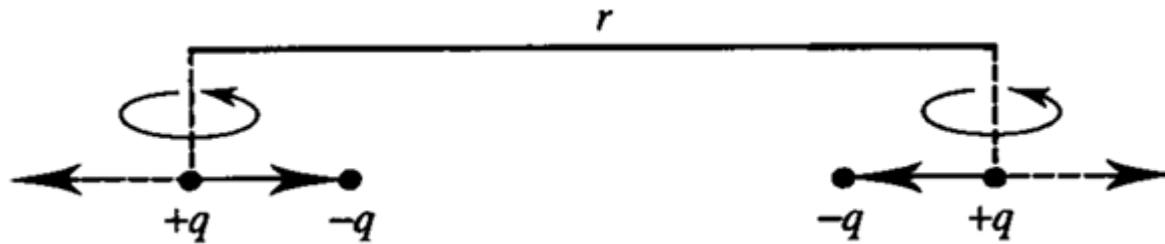
Short range (van der Waals) interactions

- If we were to study interaction between two argon atoms, we would find that the interaction energy varies as shown in the figure. As the separation is reduced from large distance, the energy decreases, passes through a minimum and then increases rapidly as the separation decreases further.
- Presence of repulsive interaction at very short distance and attractive interaction at little longer distance.
- Note that Ar atoms do not have any permanent charge, dipole or higher multipoles.
- The attractive contribution originates from dispersive forces due to instantaneous dipoles which arise during fluctuations in electron cloud.



Dispersive interactions: Drude Model

- The Drude model consists of 'molecules' with two charges, $+q$ and $-q$, separated by a distance r . The negative charge performs simple harmonic motion with frequency ω along Z-axis about the stationary positive charge.



- The force constant of the harmonic oscillator is k and mass m so that the frequency of oscillation is

$$\omega_0 = \left(\frac{k}{m} \right)^{\frac{1}{2}}$$

Ref. A. R. Leach, *Molecular Modelling*, Addison Wesley Longman (1998)

- The coordinates of negative charges are z_a and z_b for the two atoms labeled a and b. The Schrödinger wave equation for molecule a is

$$\frac{1}{m} \frac{\partial^2 \Psi_a}{\partial z_a^2} + \frac{2}{\hbar^2} \left(E_a - \frac{1}{2} k z_a^2 \right) \Psi_a = 0$$

where m is the mass of the associated with charge $-q$ and Ψ_a is the wave function of the simple harmonic oscillator (SHO) a.

Here $\frac{1}{2} k z_a^2$ is the potential energy of the oscillator. The eigenvalues are well known :

$$E_a = \left(n_a + \frac{1}{2} \right) \hbar \omega_0, \quad E_b = \left(n_b + \frac{1}{2} \right) \hbar \omega_0$$

- The total energy of system when the two molecules are infinitely apart are $E(\infty) = E_a + E_b = \hbar \omega_0$
- How does one define the intermolecular interaction energy, $v(r)$?

This is the difference in the total energy of the two particle system when they are at a distance of r apart and when they are infinitely separated $v(r) = E(r) - E(\infty)$

Let us now see that what happens when the two SHO are brought together to a finite distance r but where r is still much greater than z_a and z_b . The Schrödinger equation For such a system would be written

as:

$$\frac{1}{m} \frac{\partial^2 \Psi}{\partial z_a^2} + \frac{1}{m} \frac{\partial^2 \Psi}{\partial z_b^2} + \frac{2}{\hbar^2} \left(E - \frac{1}{2} k z_a^2 - \frac{1}{2} k z_b^2 - \frac{2 z_a z_b q^2}{4 \pi \epsilon_0 r^3} \right) \Psi = 0$$

where Ψ is the wave function for the combined two-molecule system.

We do variable transformations

$$Z_1 = \frac{z_a + z_b}{\sqrt{2}}, \quad Z_2 = \frac{z_a - z_b}{\sqrt{2}}$$

In terms of these transformed variables, the above equation will be

$$\frac{1}{m} \frac{\partial^2 \Psi}{\partial Z_1^2} + \frac{1}{m} \frac{\partial^2 \Psi}{\partial Z_2^2} + \frac{2}{\hbar^2} \left(E - \frac{1}{2} k_1 Z_1^2 - \frac{1}{2} k_2 Z_2^2 \right) \Psi = 0$$

Here the new force constants corresponding to Z_1 and Z_2 are:

$$k_1 = k - \frac{2q^2}{4\pi\epsilon_0 r^3} \quad \text{and} \quad k_2 = k + \frac{2q^2}{4\pi\epsilon_0 r^3}$$

The total energy is given by

$$E(r) = \left(n_1 + \frac{1}{2} \right) \hbar \omega_1 + \left(n_2 + \frac{1}{2} \right) \hbar \omega_2$$

which in the ground state is $E(r) = \frac{1}{2} \hbar (\omega_1 + \omega_2)$

Here ω_1 and ω_2 are

$$\omega_1 = \omega_0 \left\{ 1 - \frac{2q^2}{4\pi\epsilon_0 r^3 k} \right\}^{\frac{1}{2}}, \quad \omega_2 = \omega_0 \left\{ 1 + \frac{2q^2}{4\pi\epsilon_0 r^3 k} \right\}^{\frac{1}{2}}$$

If the fluctuations in the charge density are small as in the case when the intermolecular separation is large compared to the molecular diameter ($r \gg \sigma$, where σ is the molecular diameter) then both ω_1 and ω_2 can be expanded in terms of the binomial theorem to get:

$$E(r) = \hbar \omega_0 - \frac{q^4 \hbar \omega_0}{2(4\pi\epsilon_0)^2 r^6 k^2} + \dots$$

We get,
$$\nu_{disp} = - \frac{q^4 \hbar \omega_0}{4(4\pi\epsilon_0)^2 r^6 k^2} + \dots$$

Note that in deriving the expression for v_{disp} , it is assumed an one-dimensional oscillator. A three-dimensional analogue of this is a better model.

When a Drude molecule or the oscillator is placed in an electric field E , a force equal to qE acts on a charge to produce a displacement

z'_a . The induced dipole moment in such a case is given by $\mu_{\text{ind}} = qz'_a$

At equilibrium the force qE must be balanced by the restoring force kz'_a and therefore

$$z'_a = \frac{qE}{k}$$

Which gives $\mu_{\text{ind}} = \frac{q^2 E}{k}$

The polarizability is $\alpha = \frac{q^2}{k}$

Also, it has been seen that the most easily polarizable orbital is the outermost orbital. The energy of an electron in this orbital is given by the first ionization potential E_I which must be approximately equal to $\hbar\omega_0$.

The expression for v_{disp} from a three dimensional Drude model is:

$$v_{disp} = -\frac{3q^4 \hbar \omega_0}{4(4\pi\epsilon_0)^2 r^6 k^2}$$

Which can be transformed to $v_{disp} = -\frac{3\alpha^2 \hbar \omega_0}{4(4\pi\epsilon_0)^2}$

Note added: The above eqn should have a $1/r^6$

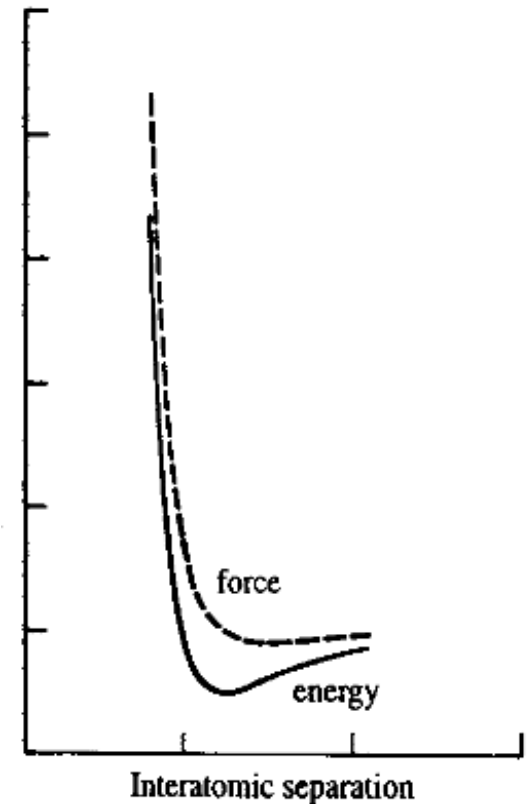
When we use the result that $E_I = \hbar\omega_0$ and $\alpha = q^2/k$. Thus, from a knowledge of the polarizability and E_I it is possible to obtain an estimate of the dispersion interaction strength.

More importantly, $v_{disp} = -\frac{C}{r^6}$

Short range repulsive interactions

This repulsive interaction is significant only when two atoms come very close to each other and thus electron cloud begin to overlap. In addition N electron cloud overlap, a number of other contributions such as Pauli repulsion, nucleus-nucleus repulsion also influence this short range repulsion.

Quantum mechanical calculations suggest an exponential $(e^{-r/\alpha})$ behavior at short distances.

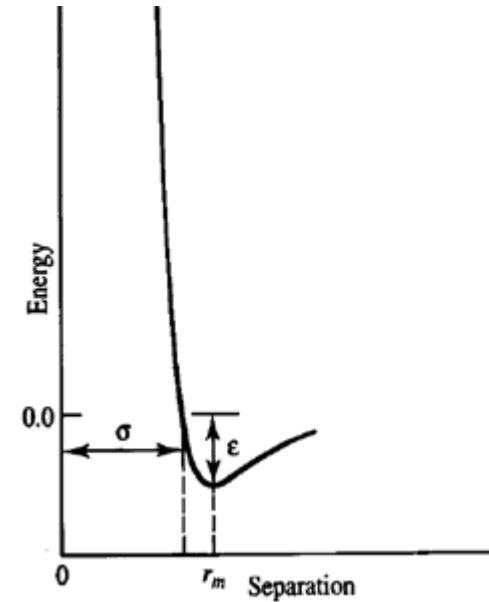


Modelling van der Waals interactions: Lennard-Jones potential

The short-range repulsive and attractive potentials are usually put in common used form known as Lennard-Jones potential.

$$v(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right]$$

The r^{-6} term is, of course, the same power-law relationship found for the theoretical calculation of dispersion energy.



There are no strong arguments in favour of the r^{-12} dependence of the repulsive part. Numerically, r^{-12} dependence has been found to be reasonable for rare gases. The 12-6 potential is largely used as model of van der Waals interaction because of its calculational simplicity.

Other forms of LJ interaction:

$$v(r) = \epsilon \left[\left(\frac{r_m}{r} \right)^{12} - 2 \left(\frac{r_m}{r} \right)^6 \right], \quad r_m = 2^{\frac{1}{6}} \sigma \quad \text{or} \quad v(r) = \frac{A}{r^{12}} - \frac{B}{r^6}$$

Non-bonded interactions: Electrostatic Contributions

Electrostatic interactions mean interactions between permanent Charges or multipoles.

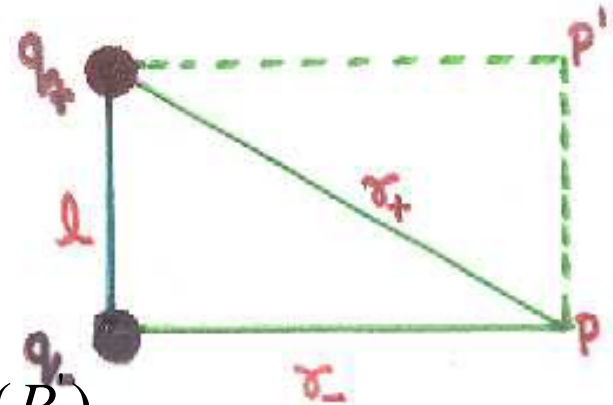
Consider a diatomic molecule :

$$q_+ = -q_- = q \quad , \quad \mu = ql$$

$$\begin{aligned} \phi(P) &= \frac{q}{r_+} - \frac{q}{r_-} = \phi_+(P) + \phi_-(P) = \phi_+(P) - \phi_+(P') \\ &= -[\phi_+(P') - \phi_+(P)] \\ &= -l \frac{[\phi_+(P') - \phi_+(P)]}{l} = -l \cdot \nabla \phi_+(P) \end{aligned}$$

In the limit $r_+ = r_- = r$, $\phi(P) = -\vec{\mu} \cdot \nabla \frac{1}{r}$

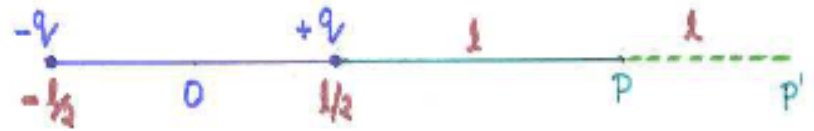
or $\phi(r) = \frac{\vec{\mu} \cdot \vec{r}}{r^3} = \frac{\mu \cos \theta}{r^2} \quad \leftarrow \text{concept of a point dipole}$



Take an exercise:

Find the electrostatic potential at points P and P' using point dipole approximation and find the percent errors.

$$\Phi(P) = \frac{q}{\ell} - \frac{q}{2\ell} = 0.5 \frac{q}{\ell}$$



Point dipole,

$$\Phi(P) = \frac{\mu}{r^2} = \frac{q\ell}{\left(3\ell/2\right)^2} = 0.44 \frac{q}{\ell}$$

Note added: The denominator of the above eqn should read $(3\ell/2)^2$

Error = 12%

At P', error = 4%

Point dipole approximation works better with increasing distance

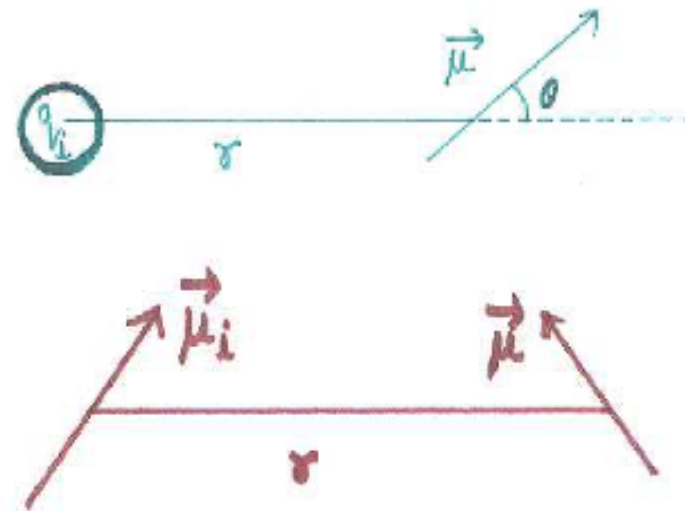
Electric field of a point dipole:

$$\begin{aligned}
 E &= -\nabla\Phi \\
 &= -\nabla\left[\frac{\vec{\mu}\cdot\vec{r}}{r^3}\right] \\
 &= -\left(\vec{\mu}\cdot\vec{r}\right)\nabla\frac{1}{r^3}-\frac{1}{r^3}\nabla\left(\vec{\mu}\cdot\vec{r}\right) \\
 &= \frac{3\left(\vec{\mu}\cdot\vec{r}\right)\vec{r}}{r^5}-\frac{\vec{\mu}}{r^3}=-T^{(2)}\cdot\vec{\mu}
 \end{aligned}$$

Where, $T^{(2)} = \frac{1}{r^3}\left[1-3\hat{r}\hat{r}\right] = -\nabla\nabla\frac{1}{r}$

$$v_{i-d} = q_i\phi(r) = \frac{q_i\mu\cos\theta}{r^2}$$

$$v_{d-d} = -\vec{\mu}_i\cdot\vec{E} = \frac{\vec{\mu}_i\cdot\vec{\mu}}{r^3} - \frac{3\left(\vec{\mu}_i\cdot\vec{r}\right)\left(\vec{\mu}\cdot\vec{r}\right)}{r^5}$$

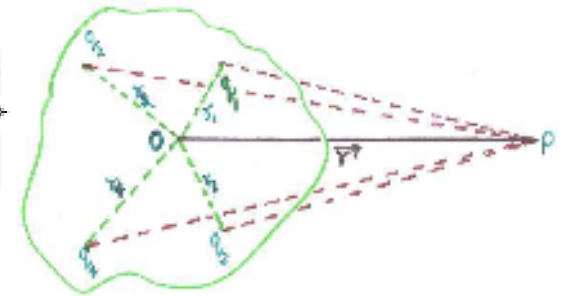


Multipole expansion scheme:

For a polyatomic molecule, $\Phi(r) = \sum_i \frac{q_i}{|r - r_i|}$

$$= \sum_i \left\{ \frac{q_i}{r_i} - q_i \vec{r}_i \cdot \nabla \left(\frac{1}{r} \right) + \frac{1}{2!} q_i (-\vec{r}_i) (-\vec{r}_i) : \nabla \nabla \frac{1}{r} + \dots \right\}$$

$$= q T^{(0)}(r) - \vec{\mu} \cdot T^{(1)}(r) + \frac{1}{2} \theta : T^{(2)}(r)$$



Where, $q = \sum_i q_i$ = Total charge, μ = dipole moment, θ = quadrupole moment

$$T^{(0)}(r) = \frac{1}{r}, \quad T^{(1)}(r) = \nabla \frac{1}{r} = -\frac{\hat{r}}{r^2}, \quad T^{(2)}(r) = \nabla \nabla \frac{1}{r} = \frac{1}{r^3} [3\hat{r}\hat{r} - 1]$$

Total potential = That of total charge at origin + that of total dipole at origin + that of total quadrupole at origin + ...

Multisite electrostatic interaction:

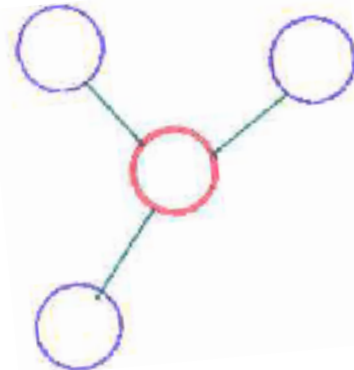
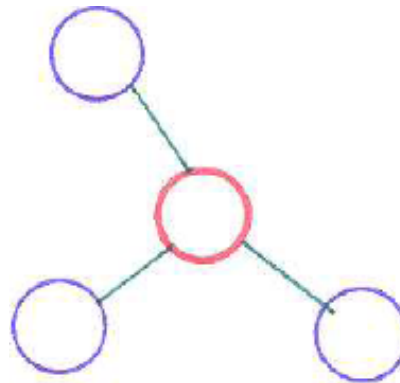
Multipole expansion scheme is alright for small molecules. For large molecules, multisite interaction scheme is practically more viable.

$$v_{12} = \sum_{s_1} \sum_{s_2} v_{s_1 s_2}(r)$$

$S_1 \Rightarrow$ sites of molecule1

$S_2 \Rightarrow$ sites of molecule2

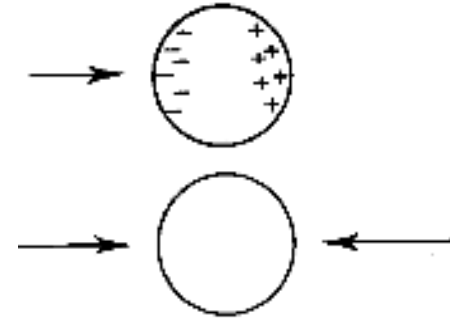
$$v_{s_1 s_2}(r) = \frac{q_{s_1} q_{s_2}}{r}$$



Other interactions:

Induction interactions: Effects of polarizability

- The charge distribution within an atom will get polarized in the presence of an electric field. Such an electric field can arise from a neighbouring molecule if it has a non-zero permanent moment for the charge distribution.



- The interaction energy of induction in presence of electric field E is

$$v_{ind} = -\int_0^E \mu \cdot dE$$

- A dipole moment can arise when a molecule of polarizability α is placed in an electric field E of a neighboring polar molecule.

$$\mu_{ind} = \alpha E$$

- The induction interaction in the presence of an electric field is therefore

$$v_{ind} = -\int_0^E \alpha E dE = -\frac{1}{2} \alpha E^2$$

Potential due to a dipolar molecule at a point is

$$\phi \propto \frac{\mu}{r^2}$$

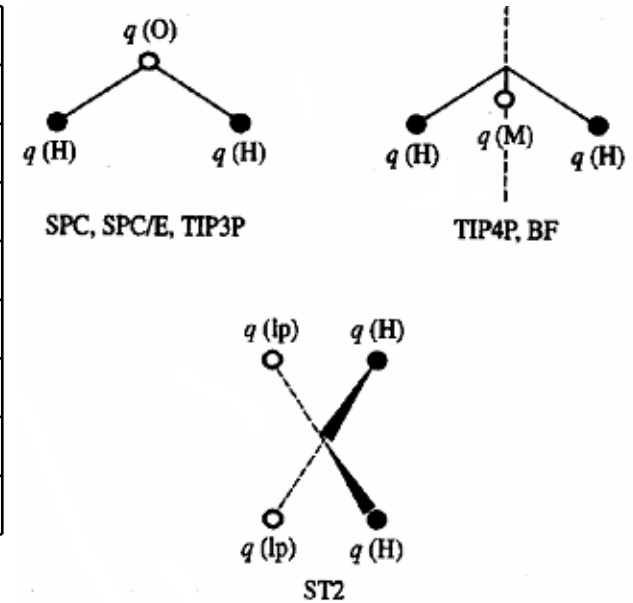
Since the electric field is the derivative of the potential, we get in the denominator r^3 for E. Therefore, U_{ind} will be

$$U_{ind} \propto \frac{\mu^2}{r^6}$$

Simple water models

The simple water models use between 3 -5 interaction sites and a rigid water geometry

	SPC	SPC/E	TIP3P	BF	TIP4P	ST2
$r(\text{OH}), \text{\AA}$	1.0	1.0	0.9572	0.96	0.9572	1.0
HOH,deg	109.47	109.47	104.52	105.7	104.52	109.47
$A \times 10^{-3}, \text{kcal } \text{\AA}^{12}/\text{mol}$	629.4	629.4	582.0	560.4	600.0	238.7
$C, \text{kcal } \text{\AA}^6/\text{mol}$	625.5	625.5	595.0	837.0	610.0	268.9
$q(\text{O})$	-0.82	-0.8472	-0.834	0.0	0.0	0.0
$q(\text{H})$	0.41	0.4238	0.417	0.49	0.52	0.2375
$q(\text{M})$	0.0	0.0	0.0	-0.98	-1.04	-0.2375
$r(\text{OM}), \text{\AA}$	0.0	0.0	0.0	0.15	0.15	0.8



Dipole moment 2.2 – 2.5 D

For another successful model see:

A.Chandra and T. Ichiye, J. Chem. Phys. **111**, 2701 (1999);
Liu and Ichiye, JPC (1996).

Force Fields for interaction with macrobodies : Reduction of variables

One example : Molecular-surface interaction

Consider a circular ring of radius x take the cross section $dx dz$

$$\text{volume} = 2\pi x dx dz$$

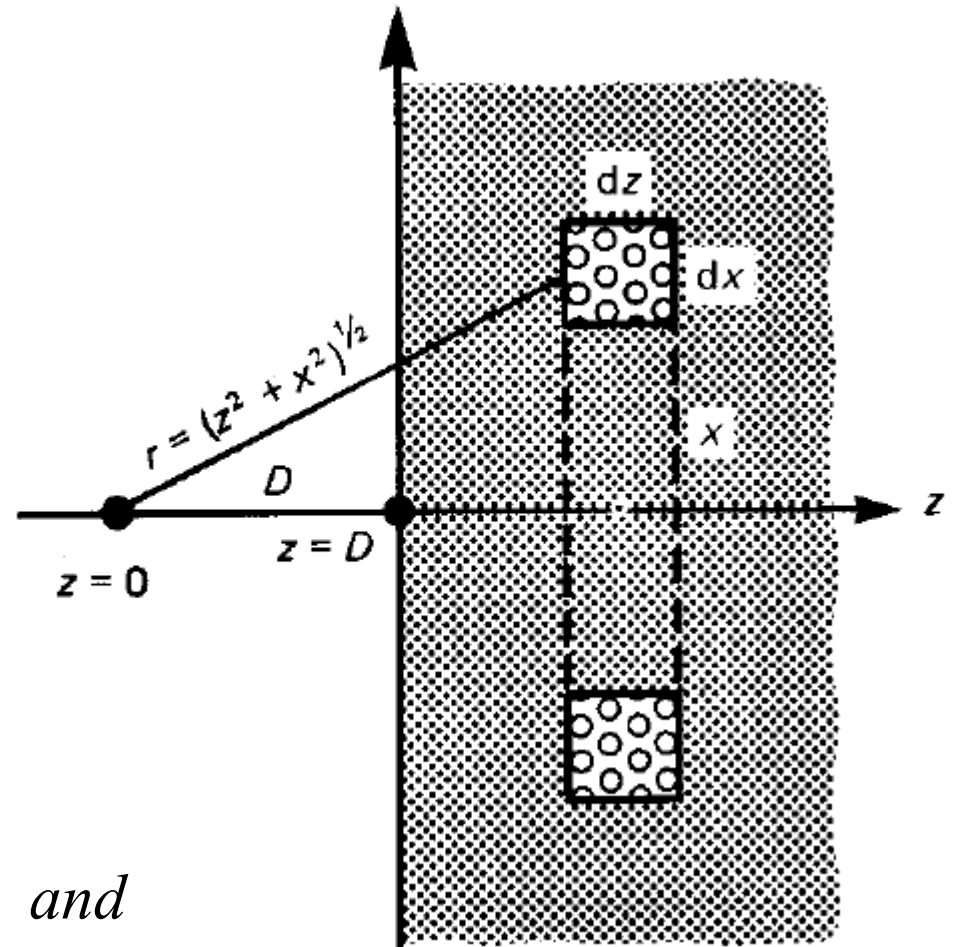
$$\text{no. of molecules} = 2\pi\rho x dx dz$$

Suppose $x' = (z^2 + x^2)$

$$dx' = 2x dx$$

$$x' = (z^2 + x^2) \quad ; \quad x = 0, \quad x' = z^2 \quad \text{and}$$

$$x = \infty, \quad x' = \infty$$



Israelachvili, *Intermolecular and surface forces*, Academic Press

$$\begin{aligned}
v_{1s}(d) &= 2\pi C\rho \int_{z=d}^{z=\infty} dz \int_{x=0}^{x=\infty} \frac{xdx}{(z^2+x^2)^{n/2}} = \frac{2\pi C\rho}{(n-2)} \int_D^{\infty} \frac{dz}{z^{(n-2)}} \\
&= \frac{2\pi C\rho}{(n-2)(n-3)} \frac{1}{D^{(n-3)}}
\end{aligned}$$

If the particle interact through LJ interaction, then

$$\begin{aligned}
v_{1s}(z) &= \frac{2\pi\rho\sigma^3}{(12-2)(12-3)} \frac{4\pi\epsilon}{\left(\frac{z}{\sigma}\right)^9} - \frac{2\pi\rho\sigma^3}{(6-2)(6-3)} \frac{4\pi\epsilon}{\left(\frac{z}{\sigma}\right)^3} \\
&= \frac{A}{z^9} - \frac{B}{z^3}
\end{aligned}$$

So, the 12-6 potential become a 9-3 potential.

See, S. Senapati and A. Chandra, JCP (1999,200), JPC (2001)

Next Lecture:

QM/MM (Basic methodology)

- Hybrid QM/MM scheme to treat quantum and classical parts of a system in a combined simulation.
- QM/MM energy schemes, additive and subtractive methods, different embedding schemes, treatment of boundaries etc.
- Results of some simple QM/MM systems
- Brief description of second hands-on session

Case studies of biological systems will be discussed by Prof. Elstner.