Molecular interaction models: 2. molecular mechanics

[One important source: Leach, Molecular Modelling: Principles and Applications, chapter 4]

- So far every potential we have described in detail on this course has been **reactive**, i.e. one which can describe the forming and breaking of covalent bonds, and thus also chemical reactions.

- In materials science one of the central fields of study is the processing of materials, for which phase changes are important. Hence in materials science potentials usually have to be reactive.

- But there is a different world, that of molecular physics and biochemistry. In molecular physics, people are interested in the behaviour of intact molecules. In conventional biochemistry, again, everything happens in a very narrow temperature interval around room temperature. In both cases *covalent bonds never break*.

- Hence an entirely different approach may be taken to potential development: the potentials do not need to be reactive
  - This means it does not matter what happens when the bond length r goes far off from its equilibrium value, since it never will.
  - The same is true for the angles between bonds θ .

- A huge set of nonreactive interatomic potentials for molecules (often also called **force fields**) have been developed by chemists, physicists and biochemists. The common term for these potentials is **molecular mechanics**, since they work well to describe the mechanical properties of molecules (elasticity, vibrations and rotations).

- Comparing this with the discussion on the REBO / Brenner potential, which can describe chemical reactions but is mostly used by physicists, one arrives at the jocular but not entirely inaccurate statement that

> **Chemists use molecular interaction models which are good at describing physics, whereas physicists use models which are good at describing chemistry.**

- Since the bond angles do not change too much, it becomes natural to devise the potentials as **explicit angular** potentials, with fixed angles between bonds.
    - This works especially well for small molecules, whose structure is known very accurately.

- But using explicit angles brings us back to the graphite vs. diamond dilemma: carbon (and other elements as well) can have many different bonding configurations. In reactive models this is described by the bond order scheme. In molecular mechanics an entirely different approach is taken: introduce several different atom types for one element.
    - E.g. “Carbon1” for C in the sp^3 hybridization, “Carbon2” for C in the sp^2 hybridization, and so on

    - In actual production-use molecular mechanics (MM) force fields the list of carbon atom types can be quite long: e.g. in the MM2, MM3 and MM4 force fields of Allinger et al it is: *“sp^3, sp^2, sp*, carbonyl, cyclopropane, radical, cyclopropene, and carbonium ion”

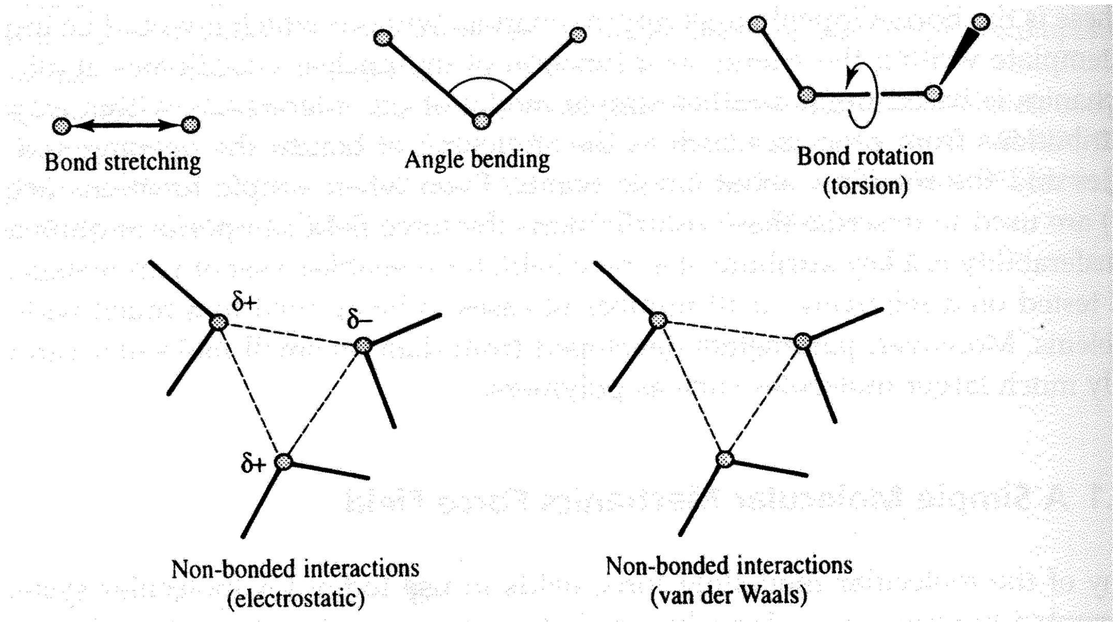
- From a fundamental physics or chemistry point of view it is of course senseless to talk about 8 different types of carbon, since there is in reality only one. But since in the MM universe chemical bonds do not break, a carbon atom will forever remain in the same bonding state, and this fundamental discrepancy does not matter.

- Also in MM the term **transferable** potential is important. A transferable MM potential is such which with parameters set for a small group of molecules can describe decently a far wider range of similar molecules.

- The transferability is particularly important, and often works well, when going from small molecules to larger ones. Since covalent bonding is inherently local in character, it is quite possible to have a set of parameters which describe covalent bonds in small molecules, applied to very much larger ones without adding new parameters for the covalent bonds.

- This allows MM force fields to describe molecules with millions of atoms.

- In this lecture package we first present the general principles of these force fields, then present some popular force fields for large molecules



- The total energy of a molecule can be given as

$$E = E_{bond} + E_{angle} + E_{torsion} + E_{oop} + E_{cross} + E_{nonbond}$$

Here:

E_{bond} describes the energy change related to a change of bond length, bond stretching, and thus is simply a pair potential V_2

E_{angle} describes the energy change associated with a change in the bond angle, i.e. is a three-body potential V_3

$E_{torsion}$ describes the torsion, i.e. energy associated with the rotation between two parts of a molecule relative to each other. It is a 4-body potential.

E_{oop} describes "out-of-plane" interactions, i.e. the energy change when one part of a molecule is out of the plane with another

E_{cross} - are cross terms between the above interaction terms.

$E_{nonbond}$ describes interaction energies which are not associated with covalent bonding.

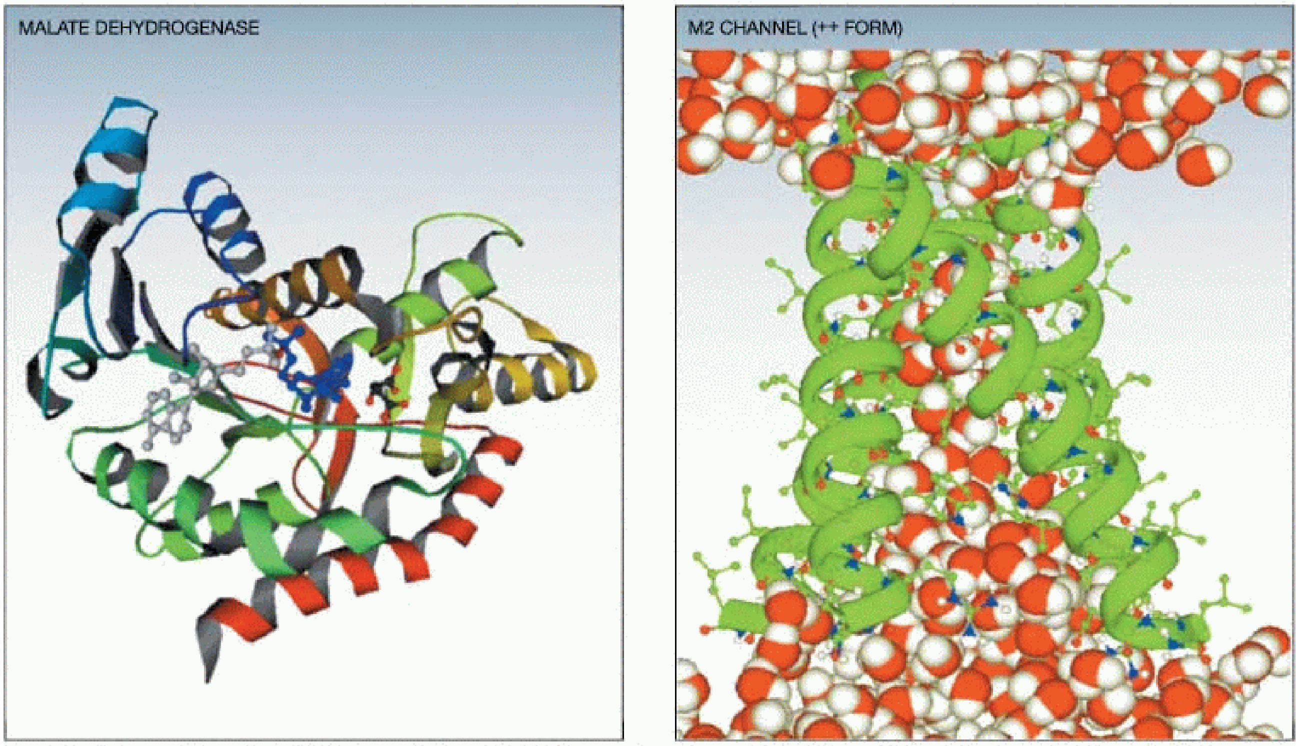
- The covalent bonds are described by the first four terms, and these are the ones which can not break. The "nonbonding" interactions can "break" in MM.
    - As noted above, the covalent bonds are local in character, and hence are the ones which can be parametrized on small molecules to describe much larger ones
    - The nonbonding interactions have longer ranges, and determine e.g. the overall structure of a large protein.

- We first discuss the "bonding" (covalent) interactions, then the nonbonding ones.

- In the following we describe the terms using notation more common on chemistry rather than the physics notation used earlier on the course.

Just as an example of what kind of systems can be studied with MM, here is a picture from IBM's Blue Gene petaflop computer project;
http://www.research.ibm.com/journal/sj/402/allen.html

Figure 1 On the left, the enzyme malate dehydrogenase is shown with the reactants for the catalytic process in place. The site where these reactants are bound, sometimes termed a *cleft*, is specifically tailored in shape and affinity to enormously accelerate this specific reaction, and to be relatively inert to other processes. On the right, the M2 proton channel of the influenza A virus is shown. This ion channel plays an essential role in infection and is the site of attack of a class of channel-blocking flu drugs. In its open state illustrated below, the water column via which protons pass through the channel is seen to be a well-defined structural feature.



Reprinted with permission, from (A) Q. Zhong, T. Husslein, P. B. Moore, D. M. Newns, P. Pattnaik, and M. L. Klein, "The M2 Channel of Influenza A Virus: A Molecular Dynamics Study," *FEBS Letters* **434**, No. 3, 265–271 (1998); (B) Q. Zhong, D. M. Newns, P. Pattnaik, J. D. Lear, and M. L. Klein, "Two Possible Conducting States of the Influenza A Virus M2 Ion Channel," *FEBS Letters* **473**, No. 2, 195–198 (2000).

Bonding interactions

The term E_{bond}

- This term describes the energy change associated with the bond length. It is a simple pair potential.

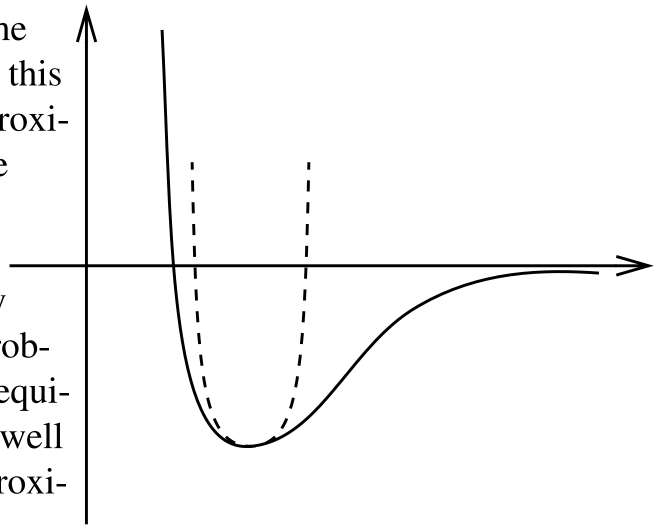
- At its simplest, it is purely harmonic, i.e.

$$E_{bond} = \sum_{bonds} \frac{1}{2} k_b (b - b_0)^2$$

where b is the bond length. If we write this term instead as

$$E_i = \sum_j \frac{1}{2} k (r_{ij} - r_0)^2$$

we see that it is the same thing as the pair potentials dealt with earlier. So this is essentially the same thing as approximating the bond as a string with the string constant k.



Although the approximation is very simple, it can be good enough in problems where we are always close to equilibrium, since any smooth potential well can always be to the first order approximated by a harmonic well.

But harmonic potentials obviously can not describe large displacements of atoms.

In solids, the harmonic approximation corresponds to the elastic regime, i.e. the one where stress is directly proportional to the strain (Hooke's law).

(A historical footnote is that Hooke presented the law already in the 17th century as "Ut tensio, sic vis" so it did not originally have much to do with interatomic potentials...)

- To improve on the bond model approximation beyond the elastic regime, one can add higher-order terms to it. Usually people go at most to fourth-order terms

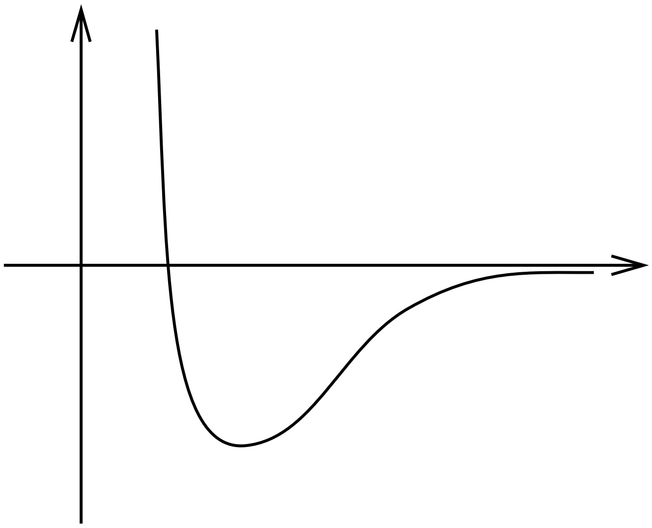
$$E_{bond} = \sum_{bonds} K_2(b-b_0)^2 + K_3(b-b_0)^3 + K_4(b-b_0)^4$$

E.g. in the MM2 field only the second- and 3-order terms are included. This has an obvious pitfall, what?

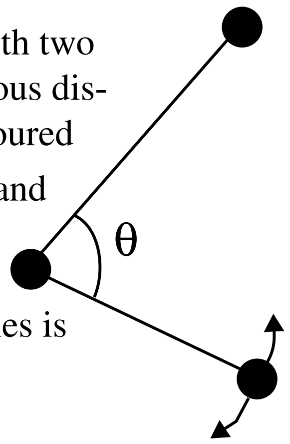
- Also the Morse potential

$$E_{bond} = \sum_{bonds} D_b\left\{1-e^{-a(b-b_0)}\right\}^2$$

is much used to describe bond energies.



Angular terms E_{angle}



- The angular terms describe the energy change associated with two bonds forming an angle with each other. To recall our previous discussion, covalent bonds have some angle which is most favoured by them - for sp^3 hybridized bonds it is ~ 109°, for sp^2 120° and so on.

  Like for bond lengths, the easiest way to describe bond angles is to use a harmonic term like

$$E_{angle} = \sum_{\theta} \frac{1}{2} H_{\theta}(\theta - \theta_0)^2$$

  where θ_0 is the equilibrium angle and H_{θ} a constant which describes the angular dependence well. This may work well up to 10° or so, but for larger angles additional terms are needed. A typical means for improvement is, surprise surprise, third-order terms and so forth, for instance

$$E_{angle} = \sum_{\theta} H_2(\theta - \theta_0)^2 + H_3(\theta - \theta_0)^3$$

  An example: by taking the simplest possible bond length and angular terms, it is already possible to describe one water molecule to some extent:

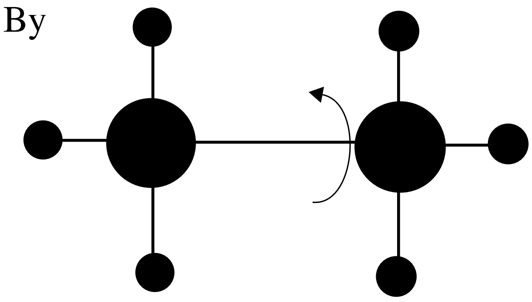
$$E_{H_2O} = K_{OH}(b - b^0_{OH})^2 + K_{OH}(b' - b^0_{OH})^2 + K_{HOH}(\theta - \theta^0_{HOH})$$

  where b and b’ are the lengths of the two bonds and θ the angle between them.

Torsional terms $E_{torsion}$

- The bond and angular terms were already familiar from the potentials for solids. In the physics and chemistry of molecules there are many important effects which can not be described solely with these terms.

  The most fundamental of these is torsion. By this, the rotations of one part of a molecule with respect to another is meant. A simple example is the rotation of two parts of the ethane molecule C_2H_6 around the central C-C carbon bond.

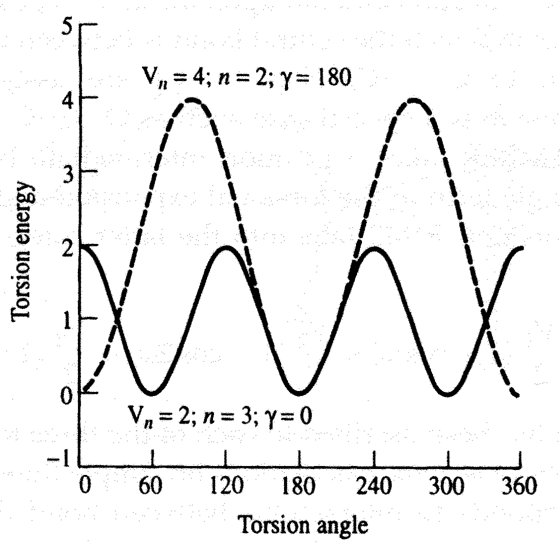
  Torsional forces can be caused by e.g. dipole-dipole-interactions and bond conjugation.

  If the angle between two parts is described by an angle ϕ, it is clear that the function f which describes the rotation should have the property $f(\phi) = f(\phi + 2\pi)$, because it is possible to do a full rotation around the central bond and return to the initial state. The trigonometric functions sin() and cos() of course fulfil this requirement, so it is natural to describe the torsional energy with a a few terms in a Fourier series:

$$E_{torsion} = V_1(1 + \cos(\phi)) + V_2(1 + \cos(2\phi)) + V_3(1 + \cos(3\phi))$$

  The first part of the torsional term V_1 - is often interpreted to be related to dipole-dipole interactions, V_2 to bond conjugation and V_3 to steric energy.

- Sometimes the torsional series also have several minima. E.g. a O-C-C-O chain found in the sugars of DNA varies with the torsion angle ϕ as in the figure to the left in the AMBER force field.



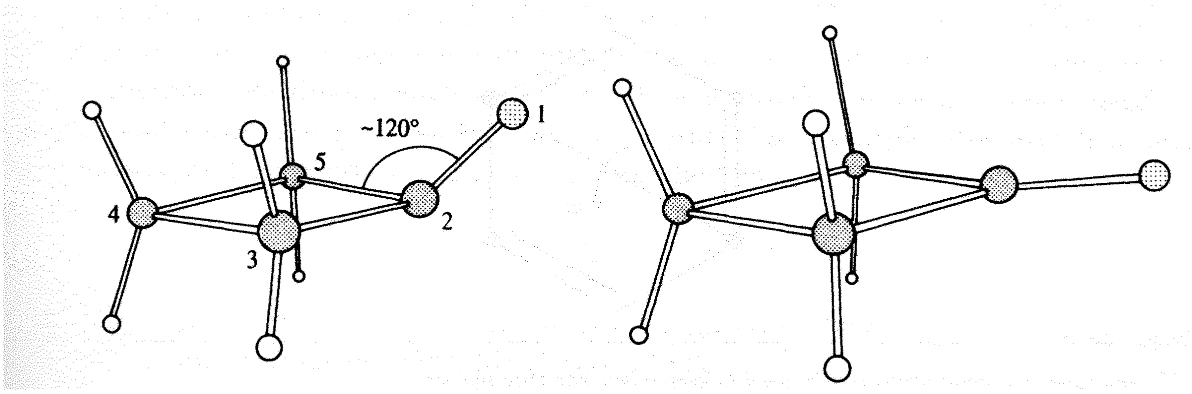
Out-of-plane terms E_{oop}

- With the out-of-plane-terms one describes the energy which in (some cases) is associated with the displacement of atoms out of the plane in which they should be. This is relevant in some (parts of) molecules where atoms are known to lie all in the same plane. The functional form can be rather simple,

$$E_{oop} = \sum_{\chi} H_{\chi}\chi^2$$

  where χ is the displacement out of the plane.

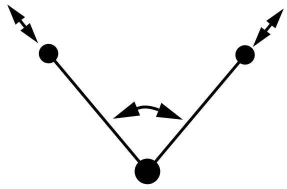
  For instance, in cyclobutane the O atom is predicted to lie out of the plane (left in figure below) rather than in the plane which is the correct configuration (right in figure):



  The out-of-plane term can also be handled mathematically in the same framework as the torsional term, by putting the atoms in the torsional 4-body term in the wrong order. One then speaks about "improper torsions". In the figure above, a normal torsion would be defined by the atoms in their bonding sequence 1-2-3-4. An improper torsion could be described by a torsional term for atoms 1-5-3-2. Since there are no bonds "1-5" and "5-3" this is not a true torsion. So improper torsions are essentially a mathematical trick to handle out-of-plane interactions.

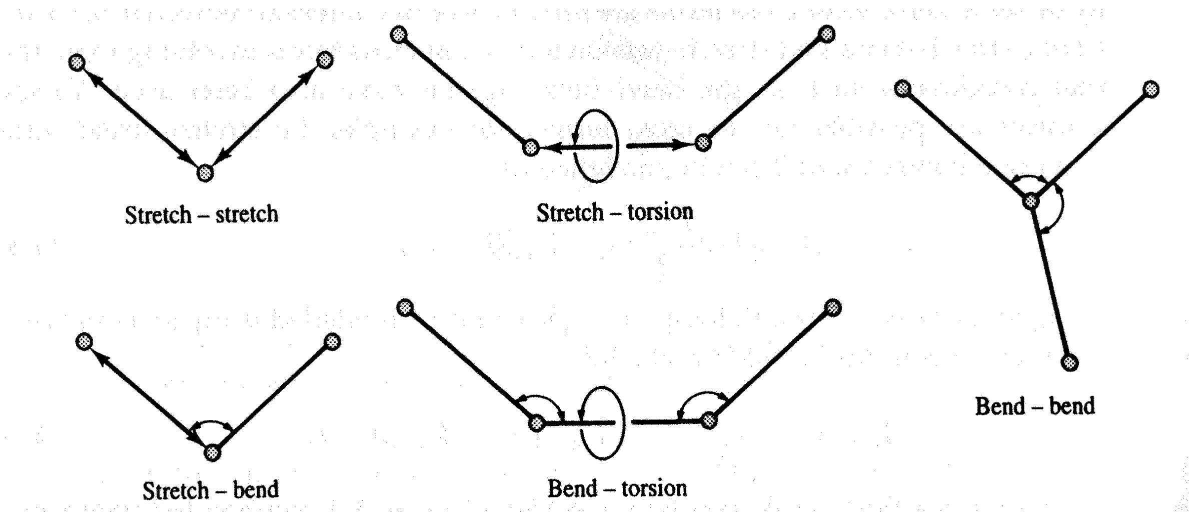
Cross terms E_{cross}

- The cross-terms are functions which contain several of the above-mentioned quantities. They could e.g. describe how when a bond angle decreases, the adjacent bonds tend to stretch (a stretch-bend term):



Since the bonding and angular terms described above are completely independent of each other, one needs a separate term to describe this effect.

In principle there should be cross terms between all bonding terms, but in practice not all are needed. For structural properties only a few may be enough, while for vibrational frequencies more are often needed.
Most cross terms are functions of two internal coordinates, such as stretch-stretch, stretch-bend, and stretch-torsion terms. The most important cross terms are believed to be the following:



- For instance, a stretch-bend term can be of the form

$$V(l_1, l_2, \theta) = \frac{k_{l_1, l_2, \theta}}{2}[(l_1 - l_{1,0}) + (l_2 - l_{2,0})](\theta - \theta_0)$$

Non-bonding terms $E_{nonbond}$

- With the non-bonding terms all effects which affect the energy of a molecule but are not covalent bonds are meant. These are e.g. van der Waals-terms, electrostatic Coulomb interactions and hydrogen bonds. For this term one can thus further divide

$$E_{nonbond} = E_{vdW} + E_{Coulomb} + E_{hbond}$$

  The van der Waals term is often a simple Lennard-Jones-potential, and $E_{Coulomb}$ a Coulomb potential for some, usually fractional, charges q_i. The hydrogen bonding term is also often of the Lennard-Jones form, although not necessarily with the 12-6 exponents.

van der Waals terms E_{vdW}

- The physical motivation for these is the same as that for noble gases: they describe induced dipole-induced dipole interactions between electrically neutral atoms or parts of a molecule. The by far most usual way to describe these is the already familiar Lennard-Jones (LJ) 12-6 potential:

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

- Note that interactions between permanent dipoles are not described by vdW terms: these are treated as Coulombic interactions.

- For molecules vdW forces can describe the interaction between two electrically neutral molecules, or interactions within a molecule.

- All atom types may have a vdW interaction with all other types. Hence if there are N atom types in a simulation, one would need N(N-1)/2 vdW interactions.

- Since this number can grow quite large (remember that there are several different types of C atoms), very frequently only elemental van der Waals parameters are defined explicitly. If we have vdW LJ parameters ε_{AA} and σ_{AA} as well as ε_{BB} and σ_{BB}, then the mixed interactions can be obtained by the Lorentz-Berthelot mixing rules as follows:

$$\sigma_{AB} = \frac{1}{2}(\sigma_{AA} + \sigma_{BB})$$

$$\varepsilon_{AB} = \sqrt{\varepsilon_{AA}\varepsilon_{BB}}$$

Ionic interactions $E_{Coulomb}$

- The topic of ionic interactions in molecules is a large one, and here we only brush the surface.

- The basic concept is that most complex molecules will have:
  - explicit fractional charges q_i
  - permanent dipoles p_i and higher multipoles

  in different parts of the molecules.

- The charges q_i will then interact via the Coulomb interaction

$$V(r_{ij}) = \frac{q_i q_j\, e^2}{4\pi\varepsilon_0\; r_{ij}}$$

  with all other charges q_j.

- The dipole interactions can either be treated by making each dipole an explicit pair of 2 charges of opposite sign, or by using the equations for dipole-charge and dipole-dipole interactions from electrodynamics.
  - The same holds for higher electrical multipoles

- The ways in which the Coulomb interaction can he handled efficiently will be dealt with later on during this course.

- Because the ionic interactions have infinite range, they can be very important in determining the overall shape of a large molecule.

- The crucial question in treating ionic interactions in molecules is how one should obtain the partial charges realistically.

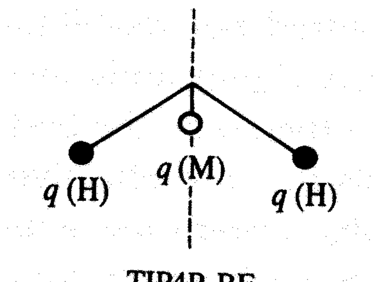
    - For relatively small systems they can derived from quantum mechanical calculations

    - For larger systems various efficient analytical methods exist

- One of the analytical schemes is the Gasteiger-Marsili approach which is based on the electronegativity of the element. The electronegativity is "the power of an atom to attract electrons to itself". The electron orbitals of each atom is assigned an electronegativity χ based on what kind of orbital it is (e.g. *sp* has a higher electronegativity than sp^3) and what the occupancy of the orbital is. An iterative procedure is then used to transfer charge between orbitals of different atoms, so that less and less charge is transferred during each iteration. This is done until a self-consistent charge distribution is obtained.

- Offhand, one could guess that the atomic charges are always placed at the locations of the atoms. However, since the electron orbitals are not necessarily symmetric, in many cases actually the charge is better placed somewhat off one of the atoms.

- An example of this: water H_2O: in some water models the charge on the oxygen is not centered where the O nucleus is, but a bit towards the H atoms. For instance the TIP4P model:



TIP4P, BF

This can be thought to be because the H atoms have attracted the O electrons towards themselves.

- The charge properties of molecules are also important when molecules are placed in a solvent, rather than vacuum. Since the solvent has a different electrical permittivity than vacuum, this can change the behaviour of the molecule significantly. The very simplest way to handle this is of course to replace ε_0 in Coulomb's law with the permittivity of the solvent $\varepsilon = \varepsilon_0\varepsilon_r$, but unfortunately this simple solution is not always good enough [Leach section 4.9.11].

Hydrogen bonding interactions E_{hbond}

- The hydrogen bonding can at its simplest be treated in molecular mechanics with Lennard-Jones potentials of the 10-12 type:

$$V(r) = \left(\frac{A}{r}\right)^{12} - \left(\frac{C}{r}\right)^{10}$$

  This function is used to model the interaction between the donor hydrogen atom and the heteroatom acceptor atom[1].

- Not all force fields include hydrogen bonding terms: others attempt to describe hydrogen bonding with electrostatic and van der Waals interactions.

1. If you are a poor physicists like me and do not quite understand what this means, don't worry: it is not required on this course.

Taking into account all of the bonding and nonbonding terms described above, except for hydrogen interactions, one can finally obtain a total energy expression which can for instance looks like

$$
\begin{aligned}
V(R) = {} & \overbrace{\sum_b D_b \left[1 - \exp(-a(b - b_0))\right]^2}^{E_{bond}} + \overbrace{\sum_\theta H_\theta (\theta - \theta_0)^2}^{E_{angle}} + \overbrace{\sum_\phi H_\phi \left[1 + s\cos(n\phi)\right]}^{E_{torsion}} \\
E_{oop} \quad & \boxed{+ \sum_\chi H_\chi \chi^2} + \sum_b \sum_{b'} F_{bb'} (b - b_0)(b' - b'_0) + \sum_\theta \sum_{\theta'} F_{\theta\theta'} (\theta - \theta_0)(\theta' - \theta'_0) \\
& + \sum_b \sum_\theta F_{b\theta} (b - b_0)(\theta - \theta_0) + \sum_\theta \sum_{\theta'} F_{\theta\theta'\phi} (\theta - \theta_0)(\theta' - \theta'_0)\cos\phi \quad E_{cross} \\
& + \sum_\chi \sum_{\chi'} F_{\chi\chi'} \chi\chi' + \sum_i \sum_{j>i} \left[\underbrace{\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}}}_{E_{vdW}} + \underbrace{\frac{q_i q_j}{r_{ij}}}_{E_{Coulomb}} \right]
\end{aligned}
$$

Some widely used force field molecular models

- In practice, most molecular modellers now use commercial models. Probably the most popular ones are those sold by AccelRys Ltd, formerly Molecular Simulations Inc. AccelRys has been formed by the fusion of numerous old companies, whence there is a some overlapping software in their packages. We go here through some of the most common of AccelRys's molecular models, describing what basic interaction models they include and to which applications they are (supposed to be) suitable. [the source are the AccelRys manuals, which are available to CSC customers from the web].

- There is of course reason to remember that the very best model for a given problem is not necessarily found from a commercial software intended for a large audience.

- AccelRys has two graphical user interfaces: **Cerius$^{\mathbf{2}}$** and **Insight**, both of which can be used to drive a large set of software, including classical and quantum mechanical models.

- Important classical models are **Discover** and **CHARMm**. In Cerius there is also in use the so called **OFF**, Open Force Field-module, which allows customers to use specialized molecular models.

- Molecular models have two main purposes: energy minimization and molecular dynamics. With minimization one strives to find the equilibrium structure of e.g. a protein, and with molecular dynamics the internal and external motion of a molecule can be examined. They are also used for other purposes, such as examining vibrational modes, molecular interactions, diffusion etc. etc.

- The AccelRys force fields can be divided in the following categories:

  - Second-generation forcefields
  - Rule-based forcefields
  - Classical forcefields
  - Special purpose forcefields

Second generation force fields

- These include e.g. CFF91, PCFF, CFF, COMPASS (“CFF family”). They are fit to a large number of chemical compounds including the elements H, C, N, O, S, P, halogens, ions, and metallic cations. In addition to experimental data, some parameters have also been fit to data derived from Hartree-Fock-calculations.

- CFF-force fields have been shown to be more accurate than the classical (“first generation”) fields in many applications. They are intended to be useable for a wide range of molecules.

- The functional form of these is

$$E_{\text{pot}} = \sum_b \left[K_2(b-b_0)^2 + K_3(b-b_0)^3 + K_4(b-b_0)^4\right] \quad \textbf{(1)}$$

$$+\sum_\theta H_2(\theta-\theta_0)^2 + H_3(\theta-\theta_0)^3 + H_4(\theta-\theta_0)^4 \quad \textbf{(2)}$$

$$+\sum_\phi \left[V_1\left[1-\cos\left(\phi-\phi_1^0\right)\right] + V_2\left[1-\cos\left(2\phi-\phi_2^0\right)\right] + V_3\left[1-\cos\left(3\phi-\phi_3^0\right)\right]\right] \quad \textbf{(3)}$$

$$+\sum_\chi K_\chi \chi^2 \ \textbf{(4)} + \sum_b\sum_{b'} F_{bb'}(b-b_0)(b'-b'_0) \ \textbf{(5)} + \sum_\theta\sum_{\theta'} F_{\theta\theta'}(\theta-\theta_0)(\theta'-\theta'_0) \ \textbf{(6)}$$

$$+\sum_b\sum_\theta F_{b\theta}(b-b_0)(\theta-\theta_0) \ \textbf{(7)} + \sum_b\sum_\phi (b-b_0)\left[V_1\cos\phi + V_2\cos 2\phi + V_3\cos 3\phi\right] \ \textbf{(8)}$$

$$+\sum_{b'}\sum_\phi (b'-b'_0)\left[V_1\cos\phi + V_2\cos 2\phi + V_3\cos 3\phi\right] \quad \textbf{(9)}$$

$$+\sum_\theta\sum_\phi (\theta-\theta_0)\left[V_1\cos\phi + V_2\cos 2\phi + V_3\cos 3\phi\right] \quad \textbf{(10)}$$

$$+\sum_\phi\sum_\theta\sum_{\theta'} K_{\phi\theta\theta'}\cos\phi\,(\theta-\theta_0)(\theta'-\theta'_0) \ \textbf{(11)} + \sum_{i>j}\frac{q_i q_j}{\varepsilon r_{ij}} \ \textbf{(12)} + \sum_{i>j}\left[\frac{A_{ij}}{r_{ij}^9} - \frac{B_{ij}}{r_{ij}^6}\right] \ \textbf{(13)}$$

- Term (13) is a Lennard-Jones-type van der Waals-term, with the exponents (9,6)

- The main areas of applications for these force fields are hydrocarbons, proteins, protein-ligand-interactions, polymers etc. The COMPASS-variety is meant for molecules in the solid state.

Rule-based for fields

- These force fields have been derived from experimentally and theoretically derived “rules” which describe the interactions. Hence the functional form is better motivated, and they should be more transferable than the classical and second-generation force fields.

- The ESFF-model strives humbly to describe all elements lighter than Rn in all cases.

- The UFF model is not this modest, but purports to describe **all** elements in all cases.

  - Of course it is clear that no classical model can describe all systems in all cases. But the idea with these fields is that they hopefully should provide somewhat reasonable force fields for cases where there doesn’t exist a good tailored model.

- The ESFF model has the following form:

$$
\begin{aligned}
E_{\mathrm{pot}} = {} & \sum_b D_b \left[1 - e^{\left(-\alpha\left(r_b - r_b^0\right)\right)}\right]^2 \qquad \textbf{(1)} \\
& + \begin{cases}
\displaystyle\sum_a \frac{K_a}{\sin^2\theta_a^0}\left(\cos\theta_a - \cos\theta_a^0\right)^2 & \textbf{(normal)} \\
\displaystyle\sum_a 2K_a(\cos\theta_a + 1) & \textbf{(linear)} \\
\displaystyle\sum_a K_a ?^{\theta_a}\cos^2\theta_a & \textbf{(perpendicular)} \\
\displaystyle\sum_a \frac{2K_a}{n^2}(1 - \cos(n\theta_a)) + 2K_a^{(-\beta(r_{13} - \rho_a))} & \textbf{(equatorial)}
\end{cases} \qquad \textbf{(2)} \\
& + \sum_\tau D_\tau \left(\frac{\sin^2\theta_1 \sin^2\theta_2}{\sin^2\theta_1^0 \sin^2\theta_2^0} + \mathrm{sign}\frac{\sin^n\theta_1 \sin^2\theta_2}{\sin^n\theta_1^0 \sin^n\theta_2^0}\cos[n\tau]\right) \qquad \textbf{(3)} \\
& + \sum_o D_o\chi^2 \;\textbf{(4)}\; + \sum_{\mathrm{nb}}\left(\frac{A_iB_j + A_jB_i}{r_{\mathrm{nb}}^9} - 3\frac{B_iB_j}{r_{\mathrm{nb}}^6}\right) \;\textbf{(5)}\; + \sum_{\mathrm{nb}}\frac{q_iq_j}{r_{\mathrm{nb}}} \;\textbf{(6)}
\end{aligned}
$$

- Note that here the pair term (1) is a Morse-potential.

  The angular term (2) is divided by the type of bond. “Normal” are the ordinary and atom ring angles. “Linear” describes atoms with bonds in a straight line. “Perpendicular” describes metal-centered atoms in molecules. “Equatorial” describes ligands (that is ~ atoms which give electrons to a metal atom and form a complex with it).

  The Lennard-Jones term (5) is again of the type (9,6).

Classical force fields

- The so called classical force fields (that is, first generation contrary to second - all of these fields are of course classical in the mathematical form, as opposed to quantum mechanical) are even more restricted in their functional form than the second-generation fields. The parameters are usually fit to experimental data, on they have most of the time been designed for macromolecules.

  The transferability of these models is usually very bad, but they can be very good for the system they have been optimized for.

- The AMBER-model is designed predominantly for proteins and DNA, but has also been used for polymers and small molecules.

  The basic functional form is

$$\boxed{\begin{aligned} E_{\mathrm{pot}} = & \underbrace{\sum_b K_2 (b - b_0)^2}_{(1)} + \underbrace{\sum_\theta H_\theta (\theta - \theta_0)^2}_{(2)} + \underbrace{\sum_\phi \frac{V_n}{2} [1 + \cos(n\phi - \phi_0)]}_{(3)} \\ & + \underbrace{\sum \varepsilon [(r^*/r)^{12} - 2 (r^*/r)^6]}_{(4)} + \underbrace{\sum q_i q_j / \varepsilon_{ij} r_{ij}}_{(5)} + \underbrace{\sum \left[\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}} \right]}_{(6)} \end{aligned}}$$

  So this really has only the first terms in the Taylor series for bonds and bond angles.

  The last Lennard-Jones (12,10)-term (6) describes hydrogen bonds.

- The CHARMm model has been designed for large macromolecules, and is considered fairly good in a large group of molecules. Its form is:

$$\begin{aligned} E_{\mathrm{pot}} = & \sum k_b (r - r_0)^2 + \sum K_\theta (\theta - \theta_0)^2 + \sum |k_\phi| - k_\phi \cos(n\phi) + \sum k_\chi (\chi - \chi_0)^2 \\ & + \sum_{\mathrm{excl}(i,j)=1} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} + \sum_{\mathrm{excl}(i,j)=1} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} \right) sw\left(r_{ij}^2, r_{\mathrm{on}}^2, r_{\mathrm{off}}^2 \right) + E_{\mathrm{constraint}} + E_{\mathrm{user}} \end{aligned}$$

  so this also only has harmonic terms. This is not necessarily a problem in biochemical applications, where the interaction energies are usually very low.

- The CVFF-force field was designed for materials science applications. It can for instance be used to describe crystals formed from small molecules. It was the original force field in the DISCOVER-program, and is hence extensively tested. The functional form is

$$
\begin{aligned}
E_{\mathrm{pot}} = {} & \underbrace{\sum_b D_b \left[1 - e^{-\alpha(b-b_0)}\right]}_{(1)} + \underbrace{\sum_\theta H_\theta (\theta - \theta_0)^2}_{(2)} + \underbrace{\sum_\phi H_\phi \left[1 + s\cos(n\phi)\right]}_{(3)} \\
& + \underbrace{\sum_\chi H_\chi \chi^2}_{(4)} + \underbrace{\sum_b \sum_{b'} F_{bb'} (b - b_0)(b' - b'_0)}_{(5)} + \underbrace{\sum_\theta \sum_{\theta'} F_{\theta\theta'} (\theta - \theta_0)(\theta' - \theta'_0)}_{(6)} \\
& + \underbrace{\sum_b \sum_\theta F_{b\theta} (b - b_0)(\theta - \theta_0)}_{(7)} + \underbrace{\sum_\phi F_{\phi\theta\theta'} \cos\phi \, (\theta - \theta_0)(\theta' - \theta'_0)}_{(8)} + \underbrace{\sum_\chi \sum_{\chi'} F_{\chi\chi'} \chi\chi'}_{(9)} \\
& + \underbrace{\sum \varepsilon \left[(r^*/r)^{12} - 2(r^*/r)^6\right]}_{(10)} + \underbrace{\sum q_i q_j / \varepsilon r_{ij}}_{(11)}
\end{aligned}
$$

So the pair potential is again a Morse-potential.

Other force fields

- Naturally there are a large group of force fields developed for specialized applications. For instance AccelRys has force fields for glasses, polyvinyl-fluorides, zeolites etc. etc.

  - From a chemistry point of view one could of course also classify the metal and semiconductor potentials we dealt with earlier as force fields for the specialized field of physics!

Overview of classical interatomic force models as a function of the branch of science