MOLECULAR MECHANICS

Molecular mechanics considers molecules as a collection of balls (atoms) held together by springs (bonds). ie Molecular Mechanics uses classical type models to predict the energy of a molecule as a function of its conformation.

In short Molecular mechanics is a force field method that uses classical models to predict the energy of a molecule as a function of its conformation

Main Applications

1) To determine equilibrium geometry and transition state
2) Relative energy between different molecules

Drawbacks

It is unsuitable for bond breaking reactions

CONCEPT OF FORCE FIELD

MM considers atoms are balls and bonds as springs. The mathematics of spring deformation can be used to describe the ability of bonds to stretch, bend and twist. Non Bonded atoms interact through van der waals forces, steric repulsion, electrostatic forces etc.

A force field is a mathematical function which returns the energy of a system as a function of the conformation of the system. Consider a molecule as a collection of atoms held together by springs. Now the forces can be written in terms of potential energy functions of various structural features such as bond lengths, bond angle, non bonded interactions etc. The force field is the combination of these potential energy terms. Hence force fields are also sometimes referred to as potentials. Thus the energy of a molecule in a force field can be written approximately as

> Energy= Stretching Energy + Bending Energy + Torsion Energy+
>
> Non- Bonded Interactions

....……………(1)

The energy E on its own has no physical meaning. Many different kinds of force- fields have been developed over the years. Some include additional energy terms that describe other

kinds of deformations. Some force-fields account for coupling between bending and stretching in adjacent bonds in order to improve the accuracy of the mechanical model.

Designing a force field

The design of force fields for molecular mechanics is guided by the following principles:

1) Nuclei and electrons are lumped into atom like particles
2) They are spherical and have a net charge
3) Interactions are based on springs and classical potentials
4) Interactions are to be pre assigned to a set of atoms
5) Interactions determine the special distribution of atom-like particles and their energies

A) Stretching energy

$$E_{str} = \Sigma \, K_b \, [r-r_o]^2 \; ....(2)$$

K_b is the parameter that controls the stiffness of the bond and is identical to force constant

r_0 is the equilibrium bond length

Unique K_b and r_0 values are assigned to each pair of bonded atoms based on their types eg [C-C , C-H , O-C] etc

This equation estimates the energy associated with vibration about the equilibrium bond length. This equation is a parabola

B) Bending energy

$$\underline{E}_{bend} = \; \Sigma \, K_\theta \, [\theta-\theta_o]^2 \; ....(3)$$

K_θ is the force constant for bending

θ_o is the ideal bond angle

θ is the actual bond angle

As in the earlier case Unique values are assigned to each pair of bonded atoms based on their types.

C) Torsion energy

The energy due to torsion is usually expressed in terms of a Fourier series

$$E\omega = \Sigma \frac{1}{2}[V_1(1 + \cos \omega) + V_2(1 + \cos 2\omega) + V_3(1 + \cos 3\omega) + \cdot \cdot \cdot] \ldots\ldots\ldots(3)$$

Where the sum is over all unique sequences of bonded atoms. In general the series is truncated at the third term, V1, V2 and V3 being chosen so that the resultant conformation agree well with experiment for a given group of molecules.

D) Non Bonded Interactions

Non bonded interactions include weak forces like Van der waals forces, London forces etc. The van der Waals energy arises from the interactions between electron clouds around two nonbonded atoms. At short range, this interaction is strongly repulsive, while at intermediate range, the interaction is attractive. As R → ∞, the interaction of course dies off to zero. The attraction is due to electron correlation: a fluctuation of the electrons on one atom produces a temporary dipole which induces a complementary dipole on the other atom. The resulting attractive force is called a "dispersion" or "London" force.

Van der Waals energies are usually computed for atoms which are connected by no less than two atoms Interactions between atoms closer than this are already accounted for by stretching and/or bending terms.

Some of the common potential functions are the Lennard Jones and Buckingham potentials

$E_{vdw}(R^{AB}) = C_e^{-DR} - E/R^6$ (Buckingham potential/hill potential equation)

One technical problem with the above "Buckingham" or "Hill" potential is that it goes to negative infinity for very small R.

$E_{vdw}(R^{AB}) = \Sigma [(R_0/R)^{12} - 2(R_0/R)^6]$ (Lennard Jones potential)

E) Electrostatic interactions

Electrostatic interactions contribute highly towards the total energy of the system. They are considered to be the most common non bonded interactions. Electrostatic contribution is modelled using a Columbic potential given as

$$E_{Coul} = \sum_{i,j=1} \frac{q_i q_j}{r_{ij}} \quad \ldots\ldots(4)$$

The electrostatic energy is a function of the charge on the non-bonded atoms, their inter atomic distance, and a molecular dielectric expression that accounts for the decrease of electrostatic interaction due to the environment (such as by solvent or the molecule itself). A linearly varying distance dependent dielectric is sometimes used to account for the increase in environmental bulk as the separation distance between interacting atoms increases.

There are two main problems in charge assignment:

1) Experimental data of charges for molecules at atom resolutions does not exist.
2) Molecular mechanics assumes that nuclei are isolated entities. The fact that nuclei share common electrons is not considered. Thus exact localization of electrons by considering atoms as *fixed* point charges is not correct.

Like van der Waals terms, electrostatic terms are typically computed for non-bonded atoms in a 1,4 relationship or further apart. Like van der Waals interactions, these are also long range interactions and dominate the computation time. While the number of bonding interactions grows linearly with molecule size, the number of non-bonded interactions grows *quadratically* with molecule size. The computation time can be reduced by cutting off the interactions after a certain distance. The van der Waals terms die off relatively quickly ($\propto R^{-6}$) and can be cut off around 10 ˚A. The electrostatic terms die off slower ($\propto R^{-1}$, although sometimes faster in practice), and are much harder to treat with cutoff.

Cross Terms

• more accurate representation of the potential energy surface (e.g. for vibrational frequencies) requires interaction terms between stretch, bend and torsion

Parameterizing from Experiment

It is clear that molecular mechanics requires many parameters. The number of potential parameters is staggering — assuming there are 30 atoms which form bonds with each other, there are $30^4/2$ torsional parameters for each term, or 1 215 000 parameters. Only the 2466 "most useful" torsional parameters are present in MM2, meaning that certain torsions cannot be described. Some programs use a set of "generic" parameters when the proper ones are unavailable — this can lead to inaccurate results. Lack of parameters parameters for different

types of atoms, chemical bonds, dihedral angles and so on. The parameter sets are usually empirical. A force field would include distinct parameters for an oxygen atom in a carbonyl functional group and in a hydroxyl group. The typical parameter set includes values for atomic mass, van der Waals radius, and partial charge for individual atoms, and equilibrium values of bond lengths, bond angles, and dihedral angles for pairs, triplets, and quadruplets of bonded atoms, and values corresponding to the effective spring constant for each potential. It can be difficult to extract the necessary parameters from experiment, especially because experiment most directly probes molecules at their equilibrium geometries. Ab initio electronic structure methods are being used more commonly to determine some of the parameters. Unfortunately van der Waals interactions are hard to get reliably from any but the largest ab initio computations, and are usually fit to experimental data for solids or liquids instead.

Heats of Formation

ΔH_f is the heat content relative to the elements at standard state at 25° C. This is a useful quantity for comparing the energies of two conformers of a molecule or two different molecules. Bond energy schemes estimate the overall ΔH_f by adding tabulated contributions from each type of bond. This works acceptably well for strain less systems. Molecular mechanics adds steric energy to the bond/structure increments to obtain better estimates of ΔH_f . Each bond is assigned a ΔH_f value, and corrections are added for larger groups (functional groups). The force field energy, which represents the steric energy, is added to this. Additionally, to go from bare energies to enthalpies, one needs to add PV (=RT) and (1/2)RT for each translational and rotational degree of freedom, for an overall enthalpy correction of 4RT. The bare molecular mechanics energy is not a meaningful quantity, because the zero of energy of each individual term was chosen as zero for convenience. Therefore different molecules have different zeros of energy until they are normalized by converting to ΔH_f.

Force fields have been parameterized using data from electronic structure calculations, e.g. the Molecular Force Field or the Quantum Mechanical Force Field. This allows the determination of force field parameters for molecules where little or no data exists. It also allows the determination of parameters in a consistent fashion. Whereas experimental data

relevant to one set of parameters may be available in the gas phase, while that for another may be available for a solid, parameters from electronic structure calculations can all be found from the same phase (usually the gas phase). This can be important as there can be large differences in molecular structure in different phases. For example the dihedral angle in biphenyl is planar in the crystal while in the liquid and gas phase it is around 45 $^{\circ}$. Full torsional potentials can be determined from electronic structure calculations. Partial atomic charges can also be found from calculations. However, there are several different methods to find charges, with little agreement between them.

The hardest parameters to determine, whether from experimental or quantum chemical data, are the Van der Waals parameters. As these determine intermolecular interactions these are highly important for determining condensed phase properties. Van der Waals parameters are often found from experimental crystal structures. They can also be calculated from high level (correlation corrected) *ab initio* calculations. However, Van der Waals parameters calculated from gas phase *ab initio* calculations can neglect interactions involving three or more atoms (3-body interactions). These can have a large contribution to the energy of a system, so neglecting these leads to large errors in the calculated values of some quantities. Another method has been used by Jorgensen *et al* in deriving the Optimized Parameters for Liquid Simulation (OPLS) parameter set. Here initial guesses were made for the Van der Waals parameters. Monte Carlo simulations were then performed on pure liquids and the Van der Waals parameters were adjusted to reproduce experimental values of thermodynamic quantities such as density and heats of vaporisation. As these parameters were fit to condensed phase properties, they implicitly include many body interactions. They are often referred to as *effective two body* potential.

Despite classical nature, force fields can mimic the behaviour of atomistic systems with an accuracy which approaches the highest level of quantum mechanical calculations in a fraction of the time. z Force fields are constructed by parameterising the potential function using either experimental data (X-ray and electron diffraction, NMR and IR spectroscopy) or ab initio and semi-empirical quantum mechanical calculations. The idea is to replace the true potential function with a simplified model valid in the region being simulated. Each time the

system is changed, the force field should be checked, and re parameterised if necessary. This approach is called molecular mechanics.

Different Force Field Methods

Class I Methods: Higher order terms and cross terms. Higher accuracy, used for small or medium sized molecules. Examples: MM1-4, EFF, and CFF.

Class II Methods: For very large molecules (e.g., proteins). Made cheaper by using only quadratic Taylor expansions and neglecting cross terms. Examples: AMBER, CHARMM, GROMOS, etc. Made even cheaper by using united atoms

1) AMBER (ASSISTED MODEL BUILDING WITH ENERGY REFINEMENT)

In order to use the AMBER force field, it is necessary to have values for the parameters of the force field (e.g. force constants, equilibrium bond lengths and angles, charges). • A fairly large number of these parameter sets exist, and are described in detail in the AMBER software user manual. Each parameter set has a name, and provides parameters for certain types of molecules

Peptide, protein and nucleic acid parameters are provided by parameter sets with names beginning with "ff" and containing a two digit year number, for instance "ff99".

GAFF (General AMBER force field) provides parameters for small organic molecules to facilitate simulations of drugs and small molecule ligands in conjunction with biomolecules.

2) CHARMM (CHEMISTRY AT HARVARD MACROMOLECULAR MECHANICS)

The CHARMM Development Project involves a network of developers throughout the world working with Martin Karplus and his group at Harvard to develop and maintain the CHARMM program. It includes

- o For united-atom- CHARMM19
- o For all-atom- CHARMM22

- o For dihedral potential corrected variantCHARMM22/CMAP
- o For DNA, RNA, and lipids - CHARMM27
- o Some force fields may be combined, for example CHARMM22 and CHARMM27 for the simulation of protein-DNA binding.

3)