Molecular Mechanics Force Fields

Basic Premise

If we want to study a protein, piece of DNA, biological membranes, polysaccharide, crystal lattice, nanomaterials, diffusion in liquids,... the number of electrons (i.e. the number of energy calculations) make quantum mechanical calculations impossible even with present-day computers.

Instead, we replace the nuclei and electrons, and their interactions, by new potential functions: ”Classical” atoms.

Based on simple physical concepts

Enables the systems under study to be VERY large (100,000 atoms).
Molecular mechanics force fields

The molecular interactions, also known as the potentials, together form a force field,

A force field is a mathematical description of the classical forces or energies between particles (atoms). Energy = function of atomic positions \((x,y,z)\)

The force field equation consists of several functions that describe molecular properties both within and between molecules

The force field also contains parameters (numbers) in the potential functions that are tuned to each type of molecule (protein, nucleic acid, carbohydrates)

There are many different force field equations and parameter sets

A force field must be simple enough that it can be evaluated quickly, but sufficiently detailed that it reproduces the key features of the physical system being modelled.
In general, force fields can be classified as either:

**Specific** (many parameters, limited applicability, high accuracy)
*Often developed in academic labs for study of specific molecular classes*
or
**Generic** (fewer parameters, more generalizations, wide applicability, poor accuracy)
*Easiest to use in point-and-click software*

Force Field Parameters can come from:

*Experimental sources (mainly from x-ray diffraction)*
or
*Theoretical calculations (mainly from QM)*

Many force fields employ similar mathematical equations but differ in the parameters used in the equations. *It is therefore extremely dangerous mix to parameters between force fields.*
Different Force Fields:

AMBER (Assisted Model Building with Energy Refinement).

CHARMM (Chemistry at HARvard using Molecular Mechanics).

GROMOS (GROenigen Molecular Simulation)

OPLS (Optimized Parameters for Large-scale Simulations)

MMFF (the Merck Molecular Force Field)

DREIDING Generic force field due to Mayo et al. (1990)

UNIVERSAL (UFF) Generic force field due to Rappeet al. (1992)

CVFF/PCFF Force fields for fluorinated hydrocarbons

MM2, MM3, MM4 Developed by Allinger et al. for calculations on small molecules

COMPASS Commercial force field marketed by Accelrys Inc.
## Different Force Fields:

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The potential functions may be divided into **bonded terms**, which give the energy contained in the internal degrees of freedom, and **non-bonded terms**, which describe interactions between molecules.

\[
E_{\text{pot}} = \sum_{\text{bonds}} V_r + \sum_{\text{angles}} V_\theta + \sum_{\text{torsions}} V_\tau + \sum_{\text{atoms}} V_{\text{vanderWaals}} + \sum_{\text{atoms}} V_{\text{electrostatics}}
\]

- Potentials between bonded atoms
- Potentials between non-bonded atoms

**Total potential Energy**, \( E_{\text{pot}} \) or \( V_{\text{tot}} \)
Force Field Potential Energy Functions

\[
V_{\text{vanderWaals}} = 4\epsilon \left[ \left( \frac{\sigma_{ij}}{R_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{R_{ij}} \right)^6 \right]
\]

\[V_{\text{Electrostatic}} = \frac{q_i q_j}{4\pi\varepsilon R_{ij}}\]

\[
V_{\text{bonds}} = \frac{1}{2} k_r (r_{ij} - r_{ij}^0)^2
\]

\[
V_{\text{angles}} = \frac{1}{2} k_\theta (\theta_{ijk} - \theta_{ijk}^0)^2
\]

\[
V_{\text{torsions}} = \frac{1}{2} \sum_n k_n (1 - \cos(n\tau))
\]

(John Lennard-Jones – 1931)

(Charles Augustin de Coulomb - 1785)

(Robert Hooke - 1660)

(Jean Baptiste Joseph Fourier – 1822)
Bond Stretch

• Approximated by a simple harmonic function about an equilibrium bond length $r_0$ with force constant $k_b$, which is defined between every pair of bonded atoms.

$$V_{b}^{\text{harm}}(r_{ij}) = \frac{k_b}{2} \left( r_{ij} - r_0 \right)^2$$

• This is a fairly poor approximation at extreme values of $r$, but bonds are usually so stiff that it works for moderate $T$.

• Accuracy can be improved by using a Morse potential, which is anharmonic, but this is considerably slower.

$$V_{b}^{\text{Morse}}(r_{ij}) = D_e \left\{ 1 - \exp \left[-a \left( r_{ij} - r_0 \right) \right] \right\}^2$$
Bond-stretching

\[ k_b (r - r_o)^2 \]
Alternatively, a power-series expansion of the Morse potential can be used.

Graphical comparison of Morse and power law potentials

Problem with harmonic approximation:

Bonds cannot break (essence of Molecular Mechanics; no bonds are broken or formed, cannot be used for chemical reactions).
Angle bend

- The bond bending energy is also approximated by a harmonic function, about an equilibrium bond angle $\theta_0$ with a force constant $k_\theta$. It is defined between every triplet of bonded atoms.

$$V_\theta(\theta_{ijk}) = \frac{k_\theta}{2}(\theta_{ijk} - \theta_0)^2$$

- The force constants for bending motion tend to be smaller than those for stretching by a factor of 5 to 7.

- Also, be aware that there may be other contributions to the bending energy from the non-bonded energies of atoms connected to the bonded pair.
Angle-bending

\[ k_\theta (\theta - \theta_0)^2 \]
Stretching or bending

\[ k_\theta (\theta - \theta_0)^2 \text{ or } k_b (r - r_0)^2 \]
Torsion Angle or Dihedral Angle Energy

The torsional energy is defined between every four bonded atoms (1-4 interactions), and depends on the torsion (aka dihedral) angle $\phi$ made by the two planes incorporating the first and last three atoms involved in the torsion.

$$V_\phi(\phi_{ijkl}) = \frac{k_\phi}{2} \left(1 + \cos 3\phi_{ijkl}\right)$$

Torsion terms account for any interactions between 1-4 atom pairs that are not already accounted for by non-bonded interactions between these atoms.

For example: they could be used to describe barriers to bond rotation from electron delocalization (double bonds or partial double bonds), or stereo-electronic effects.
Using the standard \( \cos 3\phi \) potential, there are three equilibrium positions: \( \phi = 180^\circ \) (trans state) and \( \pm 60^\circ \) (gauche states).

In practice, the energies of the gauche states are slightly different than that of the trans state, depending on the atoms involved in the torsion.
Torsion

\[ A [1 + \cos(n\tau - \phi)] \]
Torsions (cont.)

\[ A [1 + \cos(n\tau - \phi)] \]

- \( A = 2.0, n = 2.0, \phi = 0.0^\circ \)
- \( A = 1.0, n = 1.0, \phi = 90.0^\circ \)
- \( A = 1.0, n = 2.0, \phi = 0.0^\circ \)
To introduce a difference between the stabilities of the gauche and trans conformations, the torsion function can be expanded with additional terms, each with its unique contribution to the rotational energy:

\[ V_\phi(\phi) = \frac{k_1}{2} (1 + \cos \phi) + \frac{k_2}{2} (1 + \cos 2\phi) + \frac{k_3}{2} (1 + \cos 3\phi) \]

This leads to a more accurate parameterisation, but at the cost of having many more parameters to model even a modest range of molecules.
Electrostatics

Difference in electronegativity between atoms generates unequal charge distribution in a molecule.

Often electronegativity differences are represented as fractional point charges \( q \) within the molecule (normally centered at the nuclei (partial atomic charges)).

Electrostatic interaction energy is calculated as a sum of interactions between partial atomic charges, using Coulomb's law:

\[
 V_{\text{Electrostatic}} = \frac{q_i q_j}{4\pi\varepsilon R_{ij}}
\]

Naturally, this equation is also used for modeling interactions between integral charges, such as between ions.

The problem with this approach is that there is no such thing as a fractional electron, therefore there is no perfect method to derive the partial atomic charges.
Non-bonded interaction that are not electrostatic (e.g. between atoms in noble gas) are labeled van der Waals interactions

Contains **dispersion and short-range components**

**Dispersion interactions always attractive.** Arise from instantaneous dipoles that occur during fluctuations within the molecular electron cloud

**Short-range interactions are always unfavorable.** Also labeled exchange, or overlap, forces. They occur between electrons with the same spin so they do not occupy same region in space (Pauli exclusion principle)
Conceptual Basis -
dispersion energy
(electron correlation)

\[ E_2 < E_1 \]

Dispersion energy is always negative

\[ E_{\text{disp}} \sim R^{-6} (+ R^{-8} + \ldots) \]
Van der Waals potential (cont.)

\[- \frac{A_{ij}}{r_{ij}^6} + \frac{B_{ij}}{r_{ij}^{12}}\]

- Repulsion regime
- van der Waals attraction regime
- Optimum energy
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<td>Electrostatic energy is represented using a set of partial atomic charges</td>
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<td>van der Waals energy has both weakly attractive and strongly repulsive components and arises from represents electron correlation</td>
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<tr>
<td>The dispersion term is always negative whereas short-range energy is always repulsive.</td>
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<tr>
<td>Torsion terms describe bond rotational properties that arise from non-classical effects, such as electron delocalization</td>
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<td>The remaining bond and angle terms describe covalent bonding</td>
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Once we have our force field, what can we do with it?

- Energy minimisation
- Molecular Dynamics
- Conformational analysis

The accuracy of the output from all these techniques will obviously be sensitive to a greater or lesser extent on the parameterization of the force field