**Merck Molecular Force Field (MMFF)**


Drug Design: Screening of tens of thousands of compounds based on pharmacophoric models or “interactions” with the binding site of a target molecule. Accordingly, parameters for a wide variety of chemicals are required. Class I force fields have limited transferability, therefore are only parameterized for a limited number of chemical types and are of limited value for screening large numbers of compounds. Class II force fields, with their greater transferability, allow for a large number of compounds to be treated, as required for database screening. Inclusion of MMFF in CHARMM greatly facilitates the application of CHARMM in drug design.

MMFF: A Class II force field designed to be a transferable force field for pharmaceutical compounds that accurately treats conformational energetics and nonbonded interactions. This would, ideally, produce a force field that was adequate for both gas phase and condensed phase calculations.

Transferability: Application of empirical force field parameters to molecules not explicitly included during the parameter optimization.

Class I: Simplicity of form of the potential energy function limits transferability.

Class II: Extended potential energy function, including cross terms, increases transferability.

Note that transferability is relative; the more you extrapolate the less the accuracy of the force field. Even in cases when the extrapolation is small, the force field can fail. This should always be taken into account when analyzing results.
MMFF Total energy

Internal terms: bonds, angles, stretch-bend, out-of-plane bending and dihedrals
Nonbonded terms: van der Waals and Electrostatics

Internal terms

**Bond**

\[
E_{\text{bond}} = K_{\text{bond}} (r_{ij} - r_{ij}^o)^2 \cdot \left( 1 + cs (r_{ij} - r_{ij}^o) + \frac{7}{12} \left( cs^2 (r_{ij} - r_{ij}^o)^2 \right) \right)
\]

K: force constant
r_{ij}: bond length between atoms i and j
cs: cubic-stretch constant

**Angle Bending**

\[
E_{\text{angle}} = K_\theta \left( \theta_{ijk} - \theta_{ijk}^o \right)^2 \cdot \left( 1 + cb \left( \theta_{ijk} - \theta_{ijk}^o \right) \right)
\]

K: force constant
\theta_{ijk}: bond angle between atom i, j and k
cb: cubic-bend constant (-0.007°⁻¹)

**Near Linear/Linear Angle**

\[
E_{\text{angle, linear}} = K_{\text{JK linear}} \left( 1 + \cos \theta_{ijk} \right)
\]
MacKerell, MMFF notes

**Stretch-Bend**

\[ E_{stretch-bend} = (K_{ijk} (r_{ij} - r_{ij}^o) + K_{kji} (r_{kj} - r_{kj}^o)) (\theta_{ijk} - \theta_{ijk}^o) \]

\( K_{ijk} \) and \( K_{kji} \): force constants coupling the \( ij \) and \( kj \) stretches to the \( ijk \) angle

**Out-of Plane Bending** at tricoordinate centers (e.g. benzene ring)

\[ E_{OOP} = K_{OOP} (\chi_{ijk;l})^2 \]

\( \chi_{ijk;l} \): Wilson wag: angle between the bond \( jl \) and the plane \( ijk \), where \( j \) is the central atom

**Dihedral/Torsional**

\[ E_{torsion} = 0.5 (V_1 (1 + \cos \Phi) + V_2 (1 + \cos 2 \Phi) + V_3 (1 + \cos 3 \Phi)) \]

\( V \): force constants for the terms in the fourier series

\( \Phi \): dihedral angle
Nonbonded terms

Van der Waals (buffered 14-7)

\[ E_{vdW} = \varepsilon_{ij} \left( \frac{1.07R_{ij}^*}{R_{ij} + 0.07R_{ij}^*} \right)^7 \left( \frac{1.12R_{ij}^{*7}}{R_{ij}^7 + 0.07R_{ij}^{*7}} - 2 \right) \]

- \( R_{ij} \): distances between atoms i and j.
- \( R_{ij}^* \): minimum interaction energy distance between atoms i and j. (based on parameterized atomic polarizability)
- \( \varepsilon_{ij} \): well depth between atoms i and j (based on the Slater-Kirkwood expression, including polarizability and number of electrons)

Electrostatic

\[ E_{electrostatic} = \frac{q_i q_j}{D(R_{ij} + \delta)^n} \]

- \( D \): dielectric constant
- \( \delta \): electrostatic buffering constant (= 0.05)
- \( q_i \): atomic charge on atom

\[ q_i = q_i^o + \sum \omega_{KI} \]

- \( q_i^o \) is the formal atomic charge (usually 0) and \( \omega_{KI} \) are bond charge increments summed over all the covalent bonds to atom I
MMFF Parameter optimization

Internal parameters

MP2/6-31G* optimized conformations encompassing ca. 360 compounds and later tested on a set of ca. 700 conformations.
   Geometries
   Vibrational Spectra
   Conformational energetics (relative energies if minima)

Nonbond parameters

VdW terms optimized based on high level ab initio dimer calculations (MP4(SDTQ) with Sadlej’s “medium polarized” basis set (10s,6p,4d/5s,4p) contracted to 5s,3p,2d/3s,2p)

Electrostatic terms based on ca. 70 dimer interaction energies and geometries at the HF/6-31G* level.
Application of MMFF in CHARMM

1) Open and read “topology” and parameter files (15 total)

2) Structure input
   Merck format files (*.mrk)
   Mol2 format (Tripos Inc.)
     Single molecules (from SYBYL, see mmff_mol2.inp)
     MOL2 databases (output from DOCK, see mmff_database.inp)
   CHARMM format (see mmff_charmm_input.inp)
     Create “dummy” residue and generate guess coordinates
       RTF mass list must include atom types
       Explicit identification of double and triple bonds
       See top_all22_prot_mmff.inp
     Create solvated system (mmff_solvate.inp)
     Create small molecule-protein interactions
       See mmff_prot.inp and mmff_complex.inp

3) Be careful to use proper treatment of nonbond interactions
   MSHIFT
   TRUNC
   E14FAC 0.75
Read the individual atom information (AtNames, X, Y, Z, AtNum, resname, resid, segn)

Separate atoms bearing aromatic type extension (.ar), if any, from other atoms

Read bond information (IB, JB, BondType)

If BondType .eq. ar

true

=> Group all bond pairs with aromatic bond type together (BondType = ar).
=> Sort aromatic bond pairs in the increasing order of the corresponding IB.
=> Group aromatic atoms within a ring together.
=> Count the number of aromatic neighbors each aromatic atom has.
=> Go through the bond list and put the pair of both atoms with 3 neighbors (indication of fused rings) on the top of the list.

false

Start of conversion of MOL2 molecules to MMFF type
If aromatic atoms .eq. aromatic bonds

false

true

else if aromatic atoms .le. aromatic bonds

=> No fused rings
=> Assign the first aromatic bond in the list to be single. Scan the rest of the aromatic bond list, assign the bond type so that it forms Kekule-like structure.

=> At least one fused ring in the molecule
=> Assign the first fused bond to be double, the rest of the fused bonds to be double if they are in separate fused rings. If there are more than two rings fused together, assign them in accord to their connectivity.
=> Assign the bonds adjacent to the fused atoms to be single.
=> Assign the rest of the aromatic bond list with the existing aromatic bond type information to form Kekule molecules.

else if aromatic atoms .le. aromatic bonds

=> No fused rings
=> Assign the first aromatic bond in the list to be single. Scan the rest of the aromatic bond list, assign the bond type so that it forms Kekule-like structure.

End

Formal Charge (FC) assignment
FC = (valence elec) - (shared elec) - 1/2*(lone-pair elec)
MMFF capabilities in CHARMM

Energy, minimization, dynamic simulations

Structural analysis

Dynamic analysis (excluding energies via CORRelation module)

Vibrational analysis

Free energy perturbation

  limited by requirement of “chemical correctness”

  internal coordinate perturbation via TSM

  chemical perturbation via PERT, see CHARMM testcases

*mmff_clpert.inp* and *mmff_pert.inp*

Solvent analysis (see CHARMM testcase *mmff_solanal.inp*)
References


