

Merck Molecular Force Field (MMFF)

(Halgren, 1996a; Halgren, 1996b; Halgren, 1996c; Halgren, 1996d; Halgren, 1999a; Halgren, 1999b; Halgren & Nachbar, 1996)

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

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

K: force constant

r_{ij} : bond length between atoms i and j

cs: cubic-stretch constant

Angle Bending

$$E_{angle} = K_{\theta} (\theta_{ijk} - \theta_{ijk}^o)^2 \cdot (1 + cb(\theta_{ijk} - \theta_{ijk}^o))$$

K: force constant

θ_{ijk} bond angle between atom i, j and k

cb: cubic-bend constant ($-0.007^{\circ^{-1}}$)

Near Linear/Linear Angle

$$E_{angle,linear} = K_{IJKlinear} (1 + \cos\theta_{ijk})$$

Stretch-Bend

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

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

Φ : dihedral angle

Nonbonded terms

Van der Waals (buffered 14-7)

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

R_{ij} : distances between atoms i and j.

R_{ij}^* : minimum interaction energy distance between atoms i and j. (based on parameterized atomic polarizability)

ϵ_{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

δ : electrostatic buffering constant (= 0.05)

q_i : atomic charge on atom

$$q_i = q_i^o + \sum \omega_{KI}$$

q_{i0} is the formal atomic charge (usually 0) and ω_{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 (10*s*,6*p*,4*d*/5*s*,4*p*) contracted to 5*s*,3*p*,2*d*/3*s*,2*p*)

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

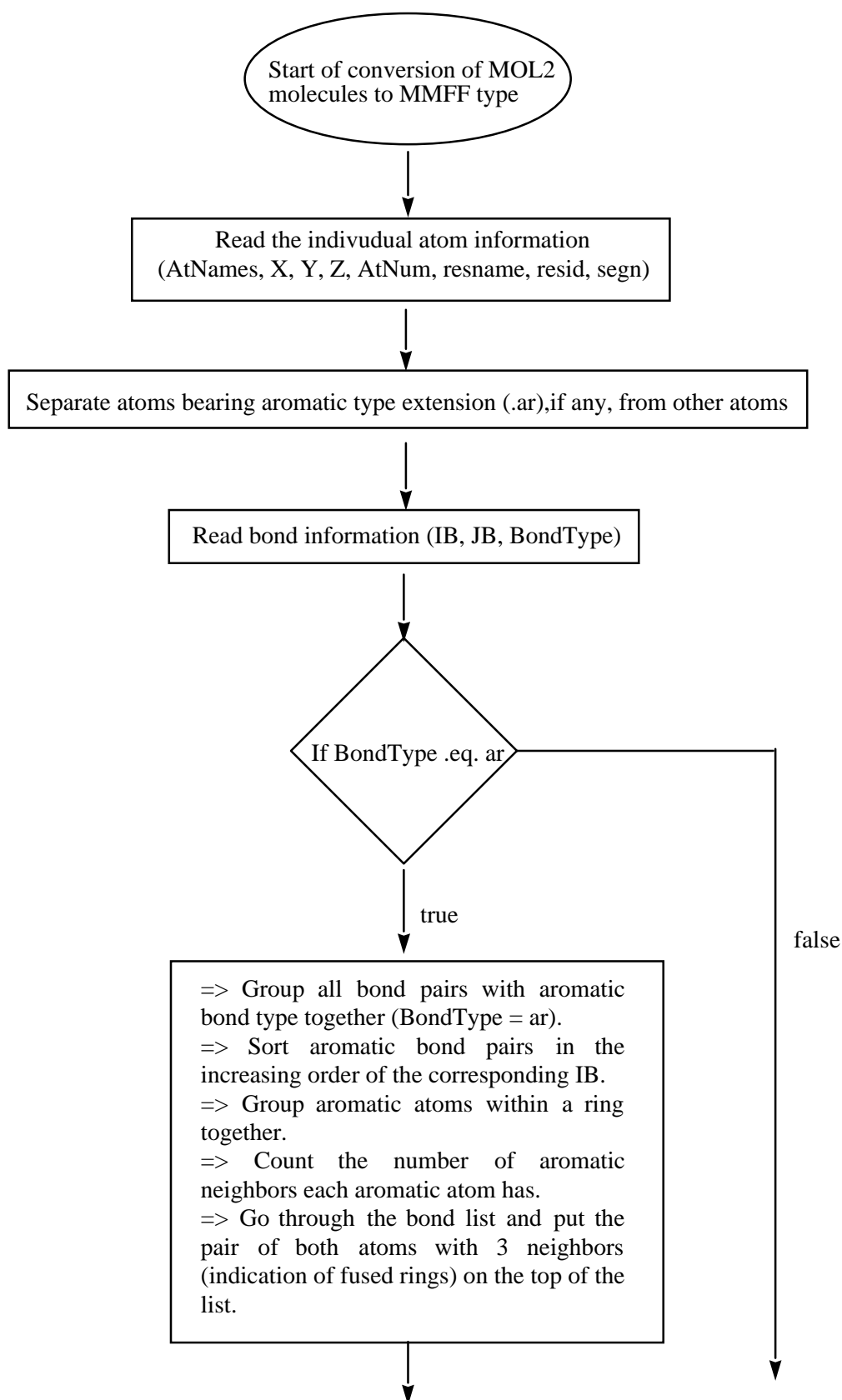
See mmff_prot.inp and mmff_complex.inp

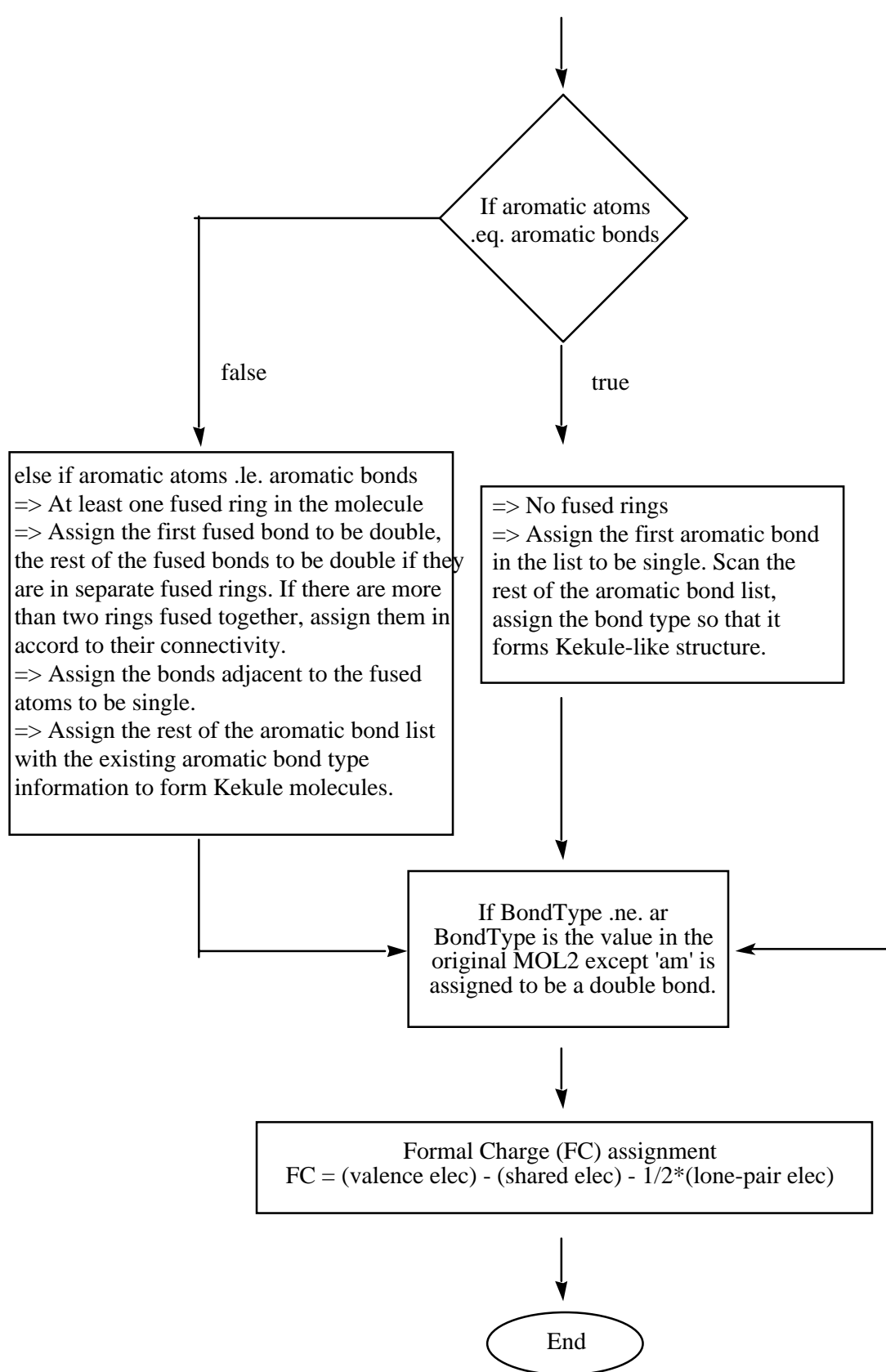
3) Be careful to use proper treatment of nonbond interactions

MSHIFT

TRUNC

E14FAC 0.75





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

- Halgren, T. A. (1996a). Merck Molecular Force Field. II. MMFF94 van der Waals and Electrostatic Parameters for Intermolecular Interactions. *J. Comp. Chem.* **17**, 520-552.
- Halgren, T. A. (1996b). Merck Molecular Force Field. III. Molecular Geometries and Vibrational Frequencies. *J. Comp. Chem.* **17**, 553-586.
- Halgren, T. A. (1996c). Merck Molecular Force Field. V. Extension of MMFF94 Using Experimental Data, Additional Computational Data and Empirical Rules. *J. Comp. Chem.* **17**, 616-641.
- Halgren, T. A. (1996d). Merck Molecular Force Field: I. Basis, Form, Scope, Parameterization and Performance of MMFF94. *J. Comp. Chem.* **17**, 490-519.
- Halgren, T. A. (1999a). MMFF VI. MMFF94s Option for Energy Minimization Studies. *J. Comp. Chem.* **20**, 720-729.
- Halgren, T. A. (1999b). MMFF VII. Characterization of MMFF94, MMFF94s, and Other Widely Available Force Fields for Conformational Energies and for Intermolecular-Interaction Energies and Geometries. *J. Comp. Chem.* **20**, 730-748.
- Halgren, T. A. & Nachbar, R. B. (1996). Merck Molecular Force Field. IV. Conformational Energies and Geometries for MMFF94. *J. Comp. Chem.* **17**, 587-615.