MM3 can be run in either standalone mode, or directly from within the SYBYL® molecular modeling suite. Many interesting characteristics of molecular structure can be investigated by molecular mechanics techniques. Some of the highlights of MM3 include:

- Molecular Dynamics
- IR Frequencies
- SYBYL Interface
- Stochastic Conformational Searches
- Thermodynamic Quantities

**MM3 Force Field**

MM3 is widely recognized as the industry’s standard for accuracy in molecular mechanics computations of hydrocarbons and simple organic functionalities. The force field equation includes the typical bond, angle, and torsion terms, as well as many cross terms to improve the fits to experimental and ab initio data. Atomic point charges get special treatment, as do hydrogen bonding groups, with charge-charge, charge-dipole, and dipole-dipole terms included in the equation. Pi systems are optimized by a VESCF calculation to determine bond orders and lengths before proceeding with optimization of the rest of the structure. The enlarged parameter set available to MM3 extends the leading performance of MM3 to more classes of small molecules encountered in today’s pharmaceutical or agrochemical research programs. In addition, a routine has been added to automatically estimate parameters for unknown atom or bond types. On-going research within Professor Allinger’s group will, in the future, extend the capabilities of MM3 to handle peptides and other biological structures. Some of the highlights of the MM3 force field are:

- Block Diagonal Newton-Raphson Minimization
- Full Newton-Raphson Minimization
- VESCF Pi System Calculation
- Metal-Coordination Compounds
- New Torsion-Stretch Terms
- Automated Parameter Estimation

**Molecular Dynamics in MM3**

MM3 performs constant temperature Molecular Dynamics simulations using Berendsen’s method for temperature coupling, and a leap-frog algorithm to integrate Newton’s equations of motion. The SHAKE algorithm allows certain bond lengths to be constrained during the simulation.

**SYBYL Interface**

Integration with the SYBYL interface allows more options for selecting functionality than previously possible. Parameter estimation is automatic, occurring whenever missing parameters are detected. The resulting final structure is loaded directly into SYBYL for more exploration, letting users combine the full set of SYBYL tools for molecular design and analysis with the best available force field.

**Stochastic Conformational Search**

MM3 provides an implementation of the Saunders method for searching conformational space and locating all conformers of a molecule. Any conformer can be used to initiate the search and additional conformers are found by randomly perturbing the atoms of the molecule and minimizing. New structures are stored and the process repeated. Checks for chirality and the stereochemistry of amide groups can be performed to preserve particular stereoisomers during the search.
Infrared Frequencies and Thermodynamic Quantities

MM3 can calculate good structures and acceptable vibrational spectra simultaneously. This option requires a full Newton-Raphson minimization and can only be performed on molecules with 120 atoms or less. The vibrational calculation uses the harmonic approximation method of Wilson, Decius, and Cross7.

Typical accuracies for frequencies are on the order of 30 to 40 cm$^{-1}$. The program also assigns the symmetry point group of the molecule, computes both Raman and IR frequencies, and can calculate intensities of the IR absorptions. The vibrational frequencies, in turn, can be used to compute a number of thermodynamic quantities, including the entropy.

MM3 also computes Heats of Formation for molecular structures. The Heat of Formation is based on the MM3 strain or steric energy plus a sum of all the bond energies. This sum is corrected for torsional, rotational, and conformational contributions, as well as branching.

Hardware and Software Requirements

MM3 can be run in either standalone mode, or called from within the SYBYL environment. MM3 requires a separate license, and runs on workstations operating under IRIX® (SGI®) or Linux® (x86).

Complementary Software

Integration of MM3 in the SYBYL expert molecular modeling environment lets users combine the full set of SYBYL tools for molecular design and analysis with industry standard force fields.

- **QSAR with CoMFA** for constructing predictive structure-activity models from a set of aligned molecules.
- **FlexX™** for flexible docking of ligands into binding sites, allowing virtual screening of compound databases.
- **FlexS™** for shape-based screening in the absence of a receptor structure, and automatic structural alignment of molecules.
- **GASP™** for automatic pharmacophore detection with full ligand flexibility and without requiring prior knowledge of pharmacophore elements or constraints.
- **DISCOtech™** for pharmacophore elucidation from precomputed conformations of active compounds that bind to the same target.

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References

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