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MOLECULAR MECHANICAL FORCE FIELDS

REVIEW & CRITICAL ANALYSIS OF MODERN DAY FORCE FIELDS WITH APPLICATION TO PROTEIN AND NUCLEIC ACID STRUCTURES

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INTRODUCTION

Force fields vary in that they are developed to be applied to different aspects of bio-organic chemistry. They are all developed differently and with specific sets of data. According to Halgren, there is still disagreement as to what form the force field should take or how it should be derived and tested (Halgren, 1996). Conversely, Allinger has the following thoughts in regard to the differences among modern day force fields (Alligner, 1996):

> They are not identical but they have certainly converged relative to the force fields in use in 1982 since they fit largely to similar data. The conclusion now is that there probably is a "best" force field, although one eventually gets down to a noise level at which arbitrary choices lead to small differences.

In this analysis, it is found that although there are significant differences in modern day force fields, they all perform at the same magnitude of precision although there are differences and each one has its own strength due to the intended application during development and the data sets used to derive and parameterize them.

The *ab initio* techniques used in developing MMFF94 and to a lesser extent CFF are closely examined as it is clear that quantum mechanical techniques will pave the way for the development of even better force fields in the future. In that sense, both Halgren and Allinger are correct—derivation of force fields based on experimental data have reached a point of convergence as the data sets themselves are finite and incomplete and undoubtedly contain experimental and systematic errors which limit the force fields, however, derivation of force fields based on quantum-mechanical physics has just begun, and although there is a point when we get down to noise, we still aren't there yet.

In this review and analysis, the following modern day force fields will be covered: MM2/MM3/MM4, AMBER, CHARMM, MMFF94, and CFF.

FORCE FIELDS

MM2/MM3 (Allinger *e tal*., 1989) /MM4 (Allinger *et al.,* 1996)

The MM family of force fields is widely used for calculations on small molecules. They are distinctive in that they distinguish the following types of carbon atom: sp^3, sp^2, sp, carbonyl, cyclopropane, radical, cyclopropene, and carbonium ion (Leach, 2001). The MM family was parameterized to fit values obtained through electron diffraction, which provide mean distances between atoms averaged over vibrational motion at room temperature (Leach, 2001). The bond stretching potential is represented by the Hooke's law to approximate the Morse curve.

 (Hooke's law)

In MM2, the Hooke's law is expanded by just a quadratic and a cubic term which causes the cubic function to pass through a maximum that is far from the reference value.

$$v(l) = \frac{k}{2}(l - l_0)^2[1 - k'(l - l_0) - k''(l - l_0) - k'''(l - l_0)^3 ...] \text{ (Hooke's law expansion)}$$

This has lead to catastrophic lengthening of bonds in some experiments. MM3 corrects this by limiting the use of the cubic contribution only when the structure is sufficiently close to its equilibrium geometry and is inside the actual potential well. According to Leach, MM3 also includes a quartic term; this eliminates the inversion problem and leads to an even better description of the Morse curve (Leach, 2001). Similar issues occurred with MM2 in regard to angle bending and were similarly corrected in MM3.

Many force fields adopt a point-charge electrostatic model where the point of origination of a charge is assigned to a particular atom. Contrastingly, the MM family assigns dipoles to the bonds in the molecule. The electrostatic energy is then given by a sum of dipole-dipole interaction energies. This approach can be overwhelming for molecules that have formal charge and which require charge-charge and charge-dipole terms to be included in the energy expression (Leach, 2001).

The MM family of force fields is often regarded as the gold standard as these force fields have been arduously derived and parameterized based on the most comprehensive and highest quality experimental data. In developing MM4, Allinger felt that MM4, in contrast to MM3 and its predecessors, has come to "something of a plateau in force field development." With MM3 they could still see that there were problems that they knew how to deal with, but with MM4 the problems are smaller, and they do not know how to deal with them any better than they have (Allinger, 1995).

AMBER 4.1 (Cornell, *et al*., 1995)

AMBER was originally parameterized against a limited number of organic systems and it has been widely used for proteins and nucleic acids. It is well characterized and well tested (Website 1, 2001). Like other force fields developed for use in modeling proteins and nucleic acids, it uses more specific atom types—specifically, according to Leach the carbon atom at the junction between a six-and a five-membered ring is assigned an atom type that is different from the carbon atom in an isolated five-membered ring such as histidine, which in turn is different from the atom type of a carbon atom in a benzene ring (Leach, 2001). Although developed for proteins and nucleic acids, AMBER has also been used for polymers and small molecules—albeit after extension of AMBER and addition of parameters. AMBER is considered generally lower in accuracy and has a limited range of applicability (Website 1, 2001). It generally gives reasonable results for gas-phase model geometries, solvation free energies, vibrational frequencies, and conformational energies.

It should be noted that AMBER employs a united atom representation—there does exist an all atom representation of AMBER as well—which differs from an all atom representation in that non-polar hydrogen atoms are not represented explicitly, but are coalesced into the description of the heavy atoms to which they are bonded. This results in significant additional speed in calculations based on AMBER compared to other force fields. AMBER also includes a hydrogen-bond term which augments the value of the hydrogen-bond energy derived from dipole-dipole interaction of the doner and acceptor groups (Leach, 2001). However, the contribution of the hydrogen-bond term is only approximately .5 kcal/mol.

Another distinction of AMBER is in regard to torsion terms. It uses general torsion parameters. According to Leach, the energy profile for rotation about a bond that is described by a general torsion potential depends solely upon the atom types of the two atoms that comprise the central bond and not upon the atom types of the terminal atoms. AMBER takes a position midway between those force fields that consistently use more terms for all torsions and those force fields that only use a single term in the torsion expansion (Leach, 2001). United atom force fields such as AMBER usually use improper torsion terms to maintain stereochemistry at chiral centers. The MM family is an example of force fields that consistently use more than one term to define the torsion expansion—specifically, they use three terms.

CHARMM22 (Mackerell & Karplus, *et al*., 1995)

CHARMM is the Chemistry at HARvard Macromolecular Mechanics force field, and was parameterized by experimental data. It has been used widely for simulations ranging from small molecules to solvated complexes of large biological macromolecules. It is also well tested and characterized (Website 1, 2001).

CHARMM performs well over a broad range of calculations and simulations, including calculation of interaction and conformation energies, geometries, local minima, time-dependent dynamic behavior, barriers to rotation, vibrational frequencies, and free energy (Website 1). In fact in a study by Karplus, he used CHARMM's ability to accurately calculate free energies to disprove a previously prevalent belief that molecular mechanical force fields are not as good as statistical methods for discerning between native and mis-folded protein structures (Lazaridis & Karplus, 1998).

CHARMM uses a flexible and comprehensive energy function:

$$E(pot) = E(bond) + E(angle) + E(torsion) + E(oop) + E(elec) + E(vdw) + E(constraint) + E(user),$$

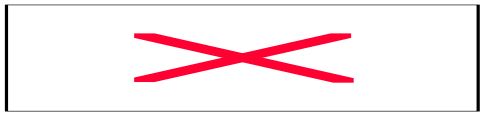
where the out-of-plane (oop) angle is defined as an improper torsion. The van der Waals term is derived from rare-gas potentials, and the electrostatic term can be scaled to mimic solvent effects (Website 1, 2001). Hydrogen-bond energy is not included as a separate term like in AMBER. Instead, hydrogen-bond energy is implicit in the combination of van der Waals and electrostatic terms.

MMFF94 (Halgren, 1996)

MMFF94 is similar to MM3 but differs in focus on application to condensed-phase processes in molecular dynamics (Halgren, 1996). MMFF94 achieves MM3-like accuracy for small molecules yet is as applicable to proteins and other systems of biological significance (Halgren, 1996).

The effort in developing MMFF94 was facilitated by a specific point of view that guided its intended use in pharmaceutical applications and called for its derivation and validation through computational approaches to develop a physically superior force field (Halgren, 1996)—MMFF94 was developed through *ab initio* techniques of quantum-mechanics at its core and verified by experimental data sets. A guiding application in the development of MMFF94 was the study of receptor-ligand interactions involving proteins and nucleic acids as receptors and a large assortment of chemical structures and ligands. Specifically, the force field must be able to quantitatively describe the ligand and the target individually as well as bound (Halgren, 1996). This requires the force field to have outstanding prediction of conformational energies and good prediction of molecular geometries if it is to avoid modeling the wrong conformations of the ligand or receptor upon binding or providing a poor estimate of the energetic cost of adopting the detailed conformation required for binding (Halgren, 1996). Furthermore, since the guiding application was the study of receptor-ligand interactions, it is easy to see why other energetic factors such as vibrational frequencies were less important to model with absolute precision.

Halgren, in developing MMFF, pioneered a novel way to more accurately model van der Waals interactions. His method improves on the Lennard-Jones potential without introducing additional complexity inherent in some other potentials used by spectroscopists. His potential was designed to be easily used in molecular mechanic calculations while still improving the quality of experimental data reproduced (Leach, 2001). His potential with a buffered 14-7 representation instead of the more common Lennard-Jones 12-6 is the following:



(Halgren van der Waals buffered 14-7 potential)

The "buffered 14-7" terminology derives from the formal 14^{th} and 7^{th} power dependencies for the repulsive and attractive terms that would be obtained if the R^*_{ij} "buffering constants" in the denominators were deleted (Halgren, 1996).

The reasons that Halgren cited for developing his functional form in the above manner are the following: 1) to keep the potential finite as the inter-atomic potential approaches zero—in contrast, the Lennard-Jones approaches infinity in this case; 2) this potential more accurately reproduces the dispersion interaction's series expansion; 3) the repulsive

component can be reduced without significantly changing the distance at which the potential crosses the energy minimum (Leach, 2001).

CFF95 (Maple & Hagler, 1994)

The CFF (consistent force field) family was developed by Halgren and the Biosym Consortium. These force fields have anharmonic and cross term enhancements. Furthermore, these force fields are derived at their core from *ab initio* methods rather than purely experimental data (see Discussion below). They were developed to reproduce peptide and protein properties and they can also be considered well tested and characterized (Website 1, 2001).

The CFF force fields use quartic polynomials for bond stretching and angle bending. For torsions they use three-term Fourier expansion. The van der Waals interactions are represented by using an inverse 9^{th}-power term for repulsive behavior instead of the more customary 12^{th}-power term.

Hagler, precursory to the development of the CFF force field, showed that no explicit hydrogen bond term is required to accurately model hydrogen-bonding interactions, as the combination of electrostatic and van der Waals calculations sufficiently captured the hydrogen-bonding contributions (Hagler, 1977). This enabled significant simplification in deriving many modern day force fields.

The development of CFF was the first major force field developed based upon *ab initio* quantum mechanical calculations on small molecules, although not as broadly applied as for the more recent MMFF94. The quantum mechanics calculations were performed on structures distorted from equilibrium in addition to the expected calculations on structures at equilibrium. This yielded a wealth of data for fitting and parameterization. The development of this force field resulted in many algorithms for the derivation of force-field parameters, in fact, Halgren used these techniques in developing MMFF94. As a result of this process, CFF has many more cross terms than other force fields which enables it to more accurately reproduce vibrational spectra.

COMPARISONS

This section is based on three comparative studies of force fields by Halgren *et al*., Beachy *et al*., and Gundertofte *et al*. The Halgren study compares primarily the MMFF94 forcefield to the other three force fields on a derivation, construction, and parameterization basis. The Gundertofte study compares the performance of the force fields with regard to accuracy in conformational energy calculations. The Beachy study compares the performance of the force fields with regard to accuracy of energetic calculations specifically for proteins and larger peptides.

Halgren *et al* Study

With regard to bond stretching, MMFF94 and MM3 use quartic expansion in which the cubic and quartic force constants are related to the quartic force constants in a predetermined way. Both therefore avoid the "cubic stretch" catastrophe discussed in the previous section which plagued predecessors of MM3. Both force fields as well as CFF use anharmonic angle bending which is a better representation than a simpler quadratic form. Trigonal centers and centers having linear idealized bond angles are taken into account differently for MMFF94 compared to the other force fields. All force fields employ the same form for torsion and stretch-bend interactions. Also, all force fields use effect pair potentials which reflect an average of the enhancement of charge distribution due to molecular polarizability (Halgren, 1995).

The most important differences and similarities between the force fields arise from their account of non-bonded contributions. MMFF94 uses the "buffered" formation to account for van der Waals forces developed by Halgren as discussed previously. AMBER, CHARMM, CFF, and MMFF94 describe hydrogen-bonding primarily through the electrostatic and van der Waals terms, although AMBER does augment this contribution through the addition of a specific hydrogen-bonding term. MM2/MM3/MM4 contrastingly, depend on a specific hydrogen-bonding term to account for a significant amount—approximately 6 kcal/mol—of stabilization energy.

Similar to MM3/MM4, CFF and MMFF94 use quartic expansion for bond stretching. But CFF and MMFF94 treat stretch-bend interactions similarly and use equivalent representations for torsion interactions. Partial atomic charges are defined in terms of bond charge increments by both force fields. Additionally, both describe electrostatic interactions only by charge-charge interactions, and both use novel van der Waals potentials—Lennard-Jones 9-6 for CFF and buffered 14-7 for MMFF94—that differ significantly from the Lennard-Jones 12-6 used by the other force fields. A major difference between CFF and MMFF94 is that CFF includes many cross terms. As discussed previously, these allow CFF to describe vibrational spectra much more accurately than MMFF94 and perhaps more accurately than any other force field. Additionally, although both CFF and MMFF94 differ from other force fields in their *ab initio* based parameterization, only MMFF94's parameterization methodology enabled nearly all of MMFF94's parameters to be determined in a mutually consistent fashion from a full set of computational data. The other force fields employ a "functional group" approach where certain parameters are fit to a portion of the available data and then frozen (Halgren, 1995). In fact, MMFF94's parameterization based on computational data has enabled it to reproduce experimental values, thus enabling it to perform equally well across systems for which experimental data does not exist (Halgren, 1995).

Beachy *et al.* Study

These force fields were primarily parameterized for study of small molecules. However, it has been difficult to demonstrate that such procedures create functions that are transferable to proteins and larger studies. In this study, correlated *ab initio* calculations have been carried out with a parallel version of the PSGVB electronic structure code to obtain relative energetics of a number of conformations of the alanine tetrapeptide, thus

this is the first study to evaluate the performance of force fields beyond that for dipeptides. The theory utilized in the study was local MP2 with cc-pVTZ(-f) correlation-consistent basis set, which has been shown to provide accurate conformational energies. Therefore, comparisons with MP2 calculations on the alanine tetrapeptide are made using LMP2/cc-pVTZ(-f) results, which are set as the benchmark for the tetrapeptides.

In this study, the most successful force fields in structure prediction are the MMFF94 and AMBER. In relative energy prediction, MMFF94 is the top force field in reducing RMS energy error for the unrestrained minima. In addition, MMFF94 displays the lowest maximum error obtained for the force fields. MM3 and CFF95 perform in the middle of the pack for both structure prediction and relative energy prediction. Interestingly, AMBER, while being good at structure prediction, is one of the worst performers in minimizing the RMS deviations from the LMP2/cc-pVTZ(-f) energies. CHARMM22 shows relatively high RMS deviations for both structure prediction and relative energy prediction.

It should be noted that this study can be criticized as being too quantum-mechanically focused by not directly utilizing any experimental data for comparison. In this regard, it is not surprising that MMFF94 performed as well as it did since it was derived and extensively parameterized through *ab initio* quantum-mechanical techniques. However, the study does provide a basis for evaluating and ranking the force fields albeit with some biases.

Gundertofte *et al* Study

This study tested force fields for accuracy in conformational energy calculations. The force fields were tested against experimental data. Overall, MMFF93 (MMFF94 was not tested) and MM3 (MM4 was not tested) were found to perform significantly better than the other force fields: CFF and AMBER, unfortunately CHARMM was not tested. Of the force fields, only MM3 and CFF were found to have functional forms and parameterization that allowed for reliable vibrational energies to be derived. For conformational energies for hydrocarbons, MM3, MMFF93, CFF, AMBER predicted within 1 kcal/mol of the experimental value. For conformational energies of oxygen-containing compounds, all but AMBER came within 1 kcal/mol. However, AMBER was the only force field in the test that gave the correct global minimum for all the oxygen-containing compounds.

It was quite apparent in this study that among the best force fields, those that depend most heavily on *ab initio* calculations for parameterization (MMFF93 and CFF) performed the best. In regards to the empirically parameterized force fields, only MM3 which has been recently re-parameterized was as good (Gundertofte, 1996).

Remarks

Based on these studies and the review and analysis of the force fields, it is clear that MMFF94 is the best force field for computing behavior of small molecules, proteins, and

nucleic acid structures. Furthermore, MMFF94 is particularly distinctive in its performance when applied to studies of binding. Although not strongly supported, it is likely that MMFF94 performs well in protein folding applications as it predicts structure as well as conformational energetics quite well. MM3/MM4's performance is also noteworthy, and it is clear why this force field has been the gold standard as it has been the long standing innovative leader for perhaps the history of force field development. In the future however, *ab initio* based force fields such as MMFF94 will certainly surpass MM3/MM4's predictive ability as is evident by MMFF94's performance.

DISCUSSION

Computational theory has enabled *ab initio* methods to provide results for small molecules that approach experimental accuracy while avoiding the possible fallacies inherent in experimental methods. Furthermore, the necessary computational data can be obtained easily and consistently over any system of interest including for those systems that lack adequate experimental data (Halgren, 1996).

The MM family of force fields was developed with high quality experimental data that had been meticulously examined for experimental error (Allinger, 1989). Likewise, AMBER and CHARMM were derived from experimental data. Contrastingly, CFF95 and MMFF94 were developed through *ab initio* methods (though validated with a wealth of experimental data). The reasons sited by Halgren for this decision in the development of MMFF94:

1. The location, extraction, and selection of good experimental data is a highly time-consuming enterprise and requires a degree of expertise his team lacked.
2. High-quality experimental data, particularly for conformational and intermolecular-interaction energies, are unavailable for a great many of the chemical structures MMFF94 must handle.

MMFF94 in fact, was patterned after CFF93, the predecessor of CFF95. In the development of the predecessor to CFF93, Hagler and his team used data obtained from a type of quantum mechanical approach known as HF/6-31G* (Hartree-Fock approximation with 6-31G* basis set) calculations. The resulting data was for Cartesian first and second derivatives, molecular dipole moments, and relative energies. Compared to experimental data, the quantum-derived data was quite good, and had two major advantages:

1. Data obtained from HF/6-31G* calculations was not biased by experimental and laboratory errors as experimental data is.
2. Since HF/6-31G* calculations could be obtained for any chemical or biological structure, there would be no holes to fill as there are with experimentally-derived data.

Furthermore, the most significant advantage for a purely quantum-derived force field compared to experimentally-derived force fields is its inherent consistency. A quantum-derived force field is certain to perform as well on all chemical and biological structures even though they may not be known; experimentally-derived force fields, however, cannot provide this assurance. In particular, use of HF/6-31G* calculated data allows parameterization in a straightforward approach that ensures appropriate balance between solvent-solvent, solvent-solute, and solute-solute interactions. A balance between these elements is necessary for accurately describing aqueous salvation as well as the energetics of binding in aqueous solution (Halgren, 1996). Of course, it should be noted that since quantum mechanics yields results that do differ consistently from experimental data, after parameterization the force field must be fit to experimental data through application of a scaling factor applied across all calculations (Website 1, 2001).

According to Leach, the development of empirical methods from *ab initio* quantum mechanical data is an approach that is already well established and looks likely to be a method that is more widely used in the future (Leach, 2001).

CONCLUSION

In a 1995 review article (Halgren, 1995), Halgren said this about the future of force field development:

> The past two years have seen a veritable beehive of activity in force field development. Remarkably, this period has seen the emergence of two new, widely parameterized bio-molecular force fields—CFF93 and MMFF94—and the completion of significant re-parameterizations of two currently widely applied force fields—CHARMM and AMBER. That these force fields differ substantially in form and in manner of derivation serves to emphasize that force field development is still as much a matter of art as of science. Some day, consensus on the form and manner of parameterization of molecular force fields may exist, but for now much remains to be learned. This is as it should be, for the problem being addressed is a hard one: to capture faithfully in a computationally tractable model enough of the real, quantum-mechanical physics to insure that a bio-molecular simulation, properly carried out, will yield a correct answer to useful precision. The way would be clearer if we knew how much physics 'enough' is.

Though we may not know how much physics is enough, we will surely be able to develop a molecular mechanics force field purely from quantum-mechanical physics if current progress is any indication of future successes. Furthermore, work toward deriving such a force field will drive progress in regard to the general application of computational techniques to biological systems.

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Website 1:
http://btcpxx.che.unibayreuth.de/COMPUTER/Software/MSI/insight9.../2_Forcefields.htm 11/23/2001