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Carbohydrate force fields

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Abstract

Carbohydrates present a special set of challenges to the generation of force fields. First, the tertiary structures of monosaccharides are complex merely by virtue of their exceptionally high number of chiral centers. In addition, their electronic characteristics lead to molecular geometries and electrostatic landscapes that can be challenging to predict and model. The monosaccharide units can also interconnect in many ways, resulting in a large number of possible oligosaccharides and polysaccharides, both linear and branched. These larger structures contain a number of rotatable bonds, meaning they potentially sample an enormous conformational space. This article briefly reviews the history of carbohydrate force fields, examining and comparing their challenges, forms, philosophies, and development strategies. Then it presents a survey of recent uses of these force fields, noting trends, strengths, deficiencies, and possible directions for future expansion.

INTRODUCTION

Developers of classical molecular dynamics (MD) force fields (FFs) appropriate to carbohydrates face a number of challenges. Not only are many of the modeled bonds strongly polar, but they are often separated from each other only by a bond or an atom. The latter characteristic manifests itself in two ways. First, and most simply, spatial charge distributions vary subtly between stereoisomers and even within conformational variants of a single monosaccharide (Sidebar Figure 1). Second is the anomeric effect, with its attendant exoanomeric effect, wherein electron-rich substituents one carbon removed from the ring oxygen prefer conformations other than what is expected on the basis of steric considerations alone. Further complication comes from the rich diversity of linear and branched structures formed by oligosaccharides. Most common carbohydrates are capable of branching at three locations in addition to the two connections needed to generate a linear chain. Each connection point contains two bonds about which torsions might vary by 60° each. In some cases, there is also a third, fully rotatable bond. When this is coupled with the fact that, in most monosaccharides, all but one carbon center is chiral, the result is an enormous number of conformational and configurational possibilities. In addition, many

saccharides are derivatized, often in ways that require adjustments in FF parameters due to changes in the local electronic structure.

Despite these challenges, carbohydrate force fields (CarbFFs) have advanced to the level that they may even outperform more sophisticated, semiempirical QM methods,¹ at least in terms of reproducing the energies associated with subtle geometrical changes in water.

Carbohydrates themselves are, of course, immensely important to almost every aspect of known life. They are products of photosynthesis and energy sources. They form fundamental building blocks for structures in plant cell walls. They are frequently present as covalent attachments on cells and proteins in eukaryotes where they are essential for normal growth and development. In the latter context, and as free oligosaccharides, they are used for identification, defense and signaling in biological pathways, implicated in health and disease alike. The ability to model them properly is therefore of immense importance to research areas as diverse as biofuels and human disease. This review will begin by briefly exploring the history of CarbFF development, explaining some of the challenges to their production. Next, the various approaches to the development of CarbFFs will be compared. Then, a survey of recent applications of classical FFs to simulations of carbohydrates will be presented. Finally, future directions for development will be suggested.

Sidebar Figure 1

Subtleties in the electrostatic characteristics of β -D-glucopyranose (left) and β -D-mannopyranose (right), whose structures differ in configuration at a single carbon center. Top (a) and bottom (b) views. The colored images are electrostatic potential (ESP) values (see legend) mapped onto an electron density isosurface ($0.002 \text{ e}/\text{\AA}^3$). Atomic charges used in CarbFFs are often developed to reproduce molecular ESPs. Accurate modeling of such subtle variations in charge distributions is one of the challenges for CarbFF development.

It should be noted that the authors of this article are developers of the GLYCAM series of CarbFFs. Although every effort has been made to present the details of other methods accurately, the reader is encouraged to peruse other recent reviews of CarbFFs and their applications.^{2–13}

HISTORY AND CLASSIFICATIONS

The following discussion refers frequently to information contained in Tables 1 and 2. These tables contain an annotated bibliography of as many CarbFFs^{14–92} as the authors were able to find using a comprehensive literature search. If any have been omitted, the omission was accidental with the exception that the tables are limited to all-atom and united-atom classical FFs intended for molecular mechanics (MM) and MD. All FFs in the tables have been used for carbohydrate simulations. Historically, there has been considerable variation among CarbFFs in terms of the number of carbohydrates employed in their development, with some being focused on a single specific monosaccharide or disaccharide. More recently, several CarbFFs have been developed with a focus on general applicability to a broad range of glycans. Although several of the FFs listed were exclusively parameterized for carbohydrates, carbohydrates have also been incorporated into broader biomolecular FFs. In general, the range of treated saccharides is expanding. For example, a few have been reported that can support the simulation of nonneutral oligosaccharides such as those containing acidic groups, or sulfates, phosphates etc.

Historical Overview

As with most endeavors, the development of CarbFFs mirrors the available technology. Advancements in the fields of computing and nuclear magnetic resonance (NMR) have had tremendous effect on CarbFF development. For example, the number of CarbFFs whose atomic charges and torsional parameters are based on quantum mechanical (QM) or semiempirical methods has increased steadily (Figure 1). QM methods allow for the assignment of parameters that cannot be determined based on existing experimental methods. That the torsion terms lagged behind charge development is almost certainly related to advances in computing power. In the mid-1980s, as computers became faster and more widely available, the use of QM calculations in the more expensive generation of torsion parameters increased. The use of QM calculations in the development of charges and torsion terms has now become almost universal.

These entirely computational parameters would need rigorous experimental data for their validation, and researchers found a wealth of such data from rapid advances in NMR. NMR data are extremely important for FF validation. This is illustrated in Figure 2, which shows two trends in the type of experimental data CarbFF developers use for validation. However, the relationship between NMR and FF development is somewhat symbiotic. Although an FF might be validated against NMR results, modeling is also often required in order to provide three-dimensional structures capable of explaining NMR data. Earlier CarbFFs did not reproduce well the sparse NMR data from flexible, solvated carbohydrates, and researchers relied more heavily on reproduction of crystallographic data. The more recent CarbFFs, when employed in MD simulations, generate molecular models that do correlate well with NMR results, and such tests are now routinely employed. That the molecular models successfully predict NMR data provides a stringent validation of CarbFFs, particularly those intended to model oligosaccharides in aqueous solution. For this reason, as has been stated previously,¹⁰ modern CarbFF development is, in large part, driven by advances in NMR data collection. Details of development and validation methodologies are discussed below.

This review includes all FFs that were identified as being parameterized using carbohydrates or carbohydrate fragments, regardless of whether they were developed exclusively for use with carbohydrates. Among CarbFFs, the trend (Figure 3) has been toward the development of FFs that are generally applicable rather than those that exclusively treat specific linkages (see Ref 74) or saccharide units (CFF^[R]/FF3, CCEM, etc.). The FFs that treat carbohydrates more generally can be categorized by design philosophy. Most of them (recent releases of CHARMM, GLY-CAM, GROMOS, OPLS, etc.) are developed in a manner consistent with simulations in a larger biological context. The rest may be identified as organic molecular FFs (TRIPOS, MM3, MM4, etc.), designed for general representations of organic molecules.

Descriptions of the various FFs (CFF, CHARMM, TRIPOS, etc.) are given in Tables 1 and 2. Not all FF names are based on acronyms despite being traditionally written in all-capital letters. Readers interested in the origins of the names should consult the individual FF references.

There are also a number of notable trends in CarbFF classes and functional forms (see section *Force Field Classifications* for details and definitions). The more recent CarbFFs are predominately Class I, as shown in Figure 4. The number of CarbFFs developed for only a subset of carbohydrates has declined sharply in recent decades (Figure 3), and none in that period were developed using a nonstandard functional form (Figure 4). The majority of recent CarbFFs include six energetic components in their functional form (Figure 5), a reflection of the dominance of the Class I formalism. The common set of Class I energetic components includes bond energies, angle energies, torsional energy corrections, Lennard-Jones interactions, electrostatic interactions and improper torsion energetic corrections.

The Anomeric Effect

The success of a CarbFF depends in large part on its treatment of a curious electronic characteristic called the anomeric effect. It was first noticed in monosaccharides, but has since been found in many other compounds and contexts. The anomeric effect manifests as an energetic preference for electron-rich substituents attached to the anomeric carbon to be oriented axially rather than equatorially (Sidebar Figure 2). This is not expected based on analogies with substituent preferences in cyclohexanes in which one of the hydrogens is replaced with some other substituent, such as a methyl or even hydroxyl group. In the latter situation, steric factors generally make an equatorial position more energetically favorable than an axial one.

Whereas in other respects the CarbFFs seem to be reaching a consensus, for example, in terms of charge assignment, there is no obvious trend with respect to treatment of the anomeric effect (Figure 6). The earliest CarbFFs, for the most part, treated the anomeric effect with special terms in their functional forms or gave it no special treatment at all. These two approaches are still in use, but so are several others, some simple and others complex. Since the anomeric effect is electronic in origin, and is not well described by a single or simple torsion term, it requires extra consideration before it can be properly included in a classical FF.

Given that the anomeric effect is of such fundamental importance, a brief discussion of the effect is warranted. The treatment here will focus only on the issues of greatest relevance to its presence in carbohydrates. Readers curious about its more general applications might start by reading of recent attempts to determine its origin,^{93–99} or one of the older and still relevant reviews of the effect in general.^{100–105}

Sidebar Figure 2

Illustration of the anomeric effect. (a) Most cyclohexane ring substituents are more stable when positioned equatorially than axially due to steric effects. (b) However, hydroxyl groups one carbon removed from a ring oxygen are more stable in the axial orientation or prefer the equatorial much less than might otherwise be expected.

A number of rationalizations for the origin for the anomeric effect have been presented. These explanations fall roughly into one of two categories. The first involves classical valence shell electron pair repulsion (VSEPR) between the lone pairs on the ring and anomeric oxygens. The second involves molecular orbital (MO) theory arguments regarding delocalization and other arrangements of electron density among the relevant orbitals. The two approaches can seem difficult to reconcile, in part because MO theory does not support the notion of lone pairs in the manner envisioned by VSEPR theory. However, there is a MO analog to the lone pair (Sidebar Figure 3) in the electrostatic potential (ESP). Whether one speaks of lone pairs or regions of negative ESP, simple electronic repulsion explains much of the anomeric effect (Sidebar Figure 4). The regions of greatest ESP are closer when the anomeric oxygen is in an equatorial configuration. This remains true regardless of the exoanomeric orientation, discussed below.

Sidebar Figure 3

Molecular orbital (MO) analog for lone pairs in water, chosen for illustration because of its simplicity. All representations except (b) are sized and positioned equivalently. (a) van der Waals representation. (b) Lone-pair drawing. (c) Constant electron density isosurface ($0.002 \text{ e}/\text{\AA}^3$). (d) Constant ESP surface ($-20 \text{ kcal}\cdot\text{mol}^{-1}\cdot\text{e}^{-1}$). (e)–(h) Four highest ground-state MOs. For those new to the concept, when comparing (c) and (d), it is useful to think of (c) as providing a spatial representation of the electrons' locations while (d)

provides a spatial representation of the combined electrons' effect. Note that only the combined electrostatic effect of the orbitals (e–h), as illustrated in (d), bears any particular resemblance to the familiar conception of water's two lone pairs. All calculations in this figure are HF/6-31G*, which is sufficient for this illustrative purpose.

However, the anomeric effect cannot be fully explained in all situations by VSEPR arguments alone, as was pointed out recently.¹⁰⁶ In the article, a series of silacyclohexanes have been substituted at the silicon atom. In these compounds, where the steric effects have been mitigated somewhat by the larger size of the silicon, calculations indicate a trend toward preferred axial orientations in all electron-rich substituents. Only the methyl-substituted moiety has strong preference for equatorial orientation. As in these cases there is, at most, only one region of enhanced ESP (Sidebar Figure 5), the explanation cannot be simple ESP repulsion. This observation inspired the authors of this manuscript to consider a monofluorinated cyclohexane. Calculations show that the axial and equatorial orientations are nearly isoergic, indicating an anomeric-like effect, possibly due to enhanced delocalization in the axial configuration. A quick electrostatic charge calculation (HF/6-31+G**) supports this, assigning a less negative charge to the axial fluorine (−0.342 e) than the equatorial (−0.396 e). Confirmation of these suggestions requires detailed calculations that are beyond the scope of this article, but it seems clear that the anomeric effect in cyclic monosaccharides depends in part on the constraints of the ring geometry.

The Exo-Anomeric Effect—In terms of oligosaccharide structure, a related tendency, the exo-anomeric effect, is of greater importance than the anomeric effect because of its influence on conformations at the glycosidic linkage. It is the tendency for atoms attached to the anomeric oxygen to orient so that the $O_{\text{ring}} - C_{\text{ano}} - O_{\text{ano}} - X$ angle is about +60° axial and −60° equatorial (Sidebar Figure 6). As with the anomeric effect, repulsion between regions of highest ESP provides the most obvious explanation for the effect. Of course, in carbohydrates, interactions between proximal hydroxyl groups can mitigate the effect, altering the exo-anomeric angle in oligosaccharides by $\pm 30^\circ$.¹⁰⁷

Force Field Classifications

Detailed information on FFs in general is available in a number of texts, for example,¹⁰⁸ and reviews.^{109–113} Herein is provided only a brief overview of the classifications important to CarbFFs: Class I (biomolecular) and Class II. Class III FFs, which might become important,

are also discussed briefly. The remaining CarbFFs are mostly miscellaneous, varying in functional form, parameterization methods, applicable molecular classes, etc. Although there has been considerable development in polarizable FFs, for example,¹¹⁴ none have been specifically intended for carbohydrates, so they will not be discussed here. An alternative method in the molecular modeling of large systems is to represent large groups of atoms with a smaller number of geometrical objects, often spheres. This approach is called coarse graining. There are coarse-grained models for carbohydrates, for example,¹¹⁵ but they will not be discussed either. Many of the concepts, functional forms and computational methods presented below and in the sidebar are generally known and can be found in molecular modeling textbooks, for example,¹⁰⁸ and many physical chemistry textbooks, for example.¹¹⁶

Sidebar Figure 4

Illustration of the electrostatic repulsion that explains much of the anomeric effect in carbohydrates. (a) The equilibrium geometries of tetrahydro-2-pyranol were determined (HF/6-31G**) for axial (left) and equatorial orientations of the hydroxyl group. The hydroxyl torsions are oriented to minimize repulsion due to the exo-anomeric effect. (b) From these structures, a minimal motif was extracted, and ESP surfaces (HF/6-311++G(2df,2p), $-20 \text{ kcal}\cdot\text{mol}^{-1}\cdot\text{e}^{-1}$) were generated for them. Note the proximity of the ESPs in the equatorial orientation compared to the axial. The volume enclosed by the ESP surface is also larger for the equatorial structure, $5.04 \text{ \AA}^3$ versus $4.17 \text{ \AA}^3$, most likely due to increased mutual repulsion between the two regions of increased ESP.

All of the FFs presented here share a few characteristics. First, they treat atoms as indivisible objects: hard or soft spheres possessing a static electric charge. Second, they treat molecular movements and interactions according to Newtonian physics. Finally, for computational efficiency the mathematical descriptions are often relevant only to systems of interest in contexts of interest. In a few cases, the models are very limited. For example, the hard-

sphere exo-anomeric effect (HSEA) model⁶³ treats monosaccharides as rigid bodies composed of van der Waals spheres, with no atomic partial charges and only the exo-anomeric torsion being free to rotate. Despite these severe limitations, the model has been effective when applied^{62,117,118} to situations where flexibility and subtle electronic effects are not critical. Readers desiring detailed descriptions of the CarbFFs considered here should consult Tables 1 and 2.

Functional Forms—The functional forms used in FFs can vary significantly. They only have in common that they describe a potential energy function that can be used in Newton's equations of motion. The majority is biomolecular in nature, employing a functional form similar to that given for Class I FFs in Eqs (1) and (2). Within these, there are also variations. For example, a number of them employ improper torsion terms or use special terms for anomeric and exo-anomeric effects. Each FF, regardless of classification, may include terms specific to the intended application of the FF.

Class I—These are also called classical, biomolecular, or quadratic FFs. As with all classical FFs, their functional forms attempt to minimize the number of mathematical operations required to model the system. However, they also try to remain general enough to treat many biologically relevant systems at or near standard ambient conditions. The primary characteristic of these FFs is that their potential energy functions use quadratic bond and angle terms. Another general feature is that the models construct molecules in a way that is intuitive to most chemists. Atoms are represented as soft-sided spheres by a van der Waals, Lennard-Jones, or similar function and are given static, partial charges. The atoms are connected to each other by bonds that are modeled as harmonic springs. Angles between bonds are also treated as harmonic springs. Subtler electronic structural effects are usually treated by including torsional terms. This class might also include terms that represent hydrogen bonding, constrain geometries to known conformations, etc. Equation (1) represents this description symbolically, and Eq. (2) represents a common functional form. If V_{Other} were taken to be an improper torsion potential term, Eq. (1) is an example of a six-component functional form as classified in Figure 5:

$$V_{\text{tot}} = V_{\text{Bonds}} + V_{\text{Angles}} + V_{\text{Torsions}} + V_{\text{vdW}} + V_{\text{Electrostatic}} [+ V_{\text{Other}}] \quad (1)$$

$$\begin{aligned} V_{\text{Typical}} = & \sum_{\text{Bonds } i,j} K_{i,j}^B (r - r_{\text{eq}})^2 \\ & + \sum_{\text{Angles } i,j,k} K_{i,j}^A (\theta - \theta_{\text{eq}})^2 \\ & + \sum_{\text{Torsions } i,j,k,l} \sum_n \frac{V_n}{2} [1 + \cos(n\varphi - \gamma n)] \quad (2) \\ & + \sum_{\text{Nonbonded } i,j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\epsilon R_{ij}} \right]. \end{aligned}$$

Sidebar Figure 5

Illustration of axial preference in the absence of ESP effects. This contribution to the anomeric effect is more likely due to delocalization than to electrostatic effects. (a) The

axial and equatorial orientations of 1-fluorosilacyclohexane are nearly isoergic.¹⁰⁶ (b) A similar calculation performed for this manuscript shows a similar effect with fluorocyclohexane (MP2/6-311++G(2df,2p)), with the two orientations being nearly isoergic ($E_{\text{ax}} - E_{\text{eq}} = 0.05$ kcal/mol).

Sidebar Figure 6

Illustration of the electrostatic origin of the exo-anomeric effect for both axial (a) and equatorial (b) geometries. Images in (a) are differently oriented from those in (b) to more clearly show the ESP in relation to atomic positions. The leftmost images are the preferred orientations. The calculations used to generate these figures are equivalent to those described in Sidebar Figure 4. Torsion angles are for $\text{O}_{\text{ring}} - \text{C}_{\text{ano}} - \text{O}_{\text{ano}} - \text{H}$.

In Eq. (2), r is the distance between the centers of bonded atoms i and j , with r_{eq} being the equilibrium distance. Similarly, θ is the angle made by bonded atoms i , j , and k , with θ_{eq} being the equilibrium angle. K^A and K^B represent harmonic spring constants associated with angle bending and bond stretching. The third summation corrects molecular energies for torsions around bonds. Here, the plane ijk makes angle ϕ with the plane jkl . For a rotation of order n , the constants V_n and γ_n indicate the magnitude and phase shift, respectively. The first two terms inside the last summation describe the Lennard-Jones potential between nonbonded atoms i and j separated by R_{ij} . The constants A_{ij} and B_{ij} define the shape of the potential. The last term represents the ESP between those same nonbonded atoms, with q_i and q_j being the charges on atoms i and j , respectively.

Class II—Class II FFs are very similar to Class I FFs in spirit and in terms of the basic molecular model. The difference is that their functional forms are more complex, with a view toward treating a wider range of ensemble conditions and electronic effects not well handled by Class I FFs. Typically, they employ anharmonic potentials (Sidebar Figure 7 and Sidebar Equation 1) and energetic cross terms. For example, a Class II CarbFF may include a term to describe the relationship between stretches and torsions associated with the anomeric center.⁸⁹ The functional forms in these FFs are not always neat or intuitive. They may include forms designed to facilitate reproduction of observables with little concern for theoretical or physical basis. Of course, while the complexity may result in better models, it also adds computational expense.

Sidebar Figure 7

Comparison of a harmonic (quadratic, blue) and an-harmonic (Morse, red) potential. Both describe an O–H stretch. The harmonic curve uses parameterization from GLYCAM06.⁵¹ The Morse potential is based on experimentally determined values for methanol.¹¹⁹ The green inset is a Maxwell–Boltzmann distribution of kinetic energies at 300 K. Although the anharmonic potential deviates from the harmonic even at very low energies, this is rarely an issue in Class I simulations: they typically freeze bonds involving hydrogen as this greatly enhances computational speed.

Class III—Class III FFs were originally suggested by Allinger.^{108,120} These FFs attempt to mimic subtle electronic effects that are not well treated with torsional corrections or cross-terms. The suggestion was prompted by attempts to model the effects of hyperconjugation for inclusion in the MM4¹²⁰ FF. Hyperconjugation occurs, for example, when proximal sigma and pi orbitals cause bonds to lengthen or contract in ways that are not well explained by steric and electrostatic factors. In a sense, many CarbFFs have Class III characteristics in that they model the anomeric and exo-anomeric effects, which arise from relatively subtle electronic effects. However, since CarbFFs generally do not extend these higher-level treatments beyond these two effects, they are not identified as Class III. In the search made for this review, no Class III CarbFFs were found, but there are reasons for which they might

be developed. For example, a Class III CarbFF might include a term to vary atomic charges as a function of ring geometry.

Miscellaneous—A number of FFs do not fall easily into Class I, II or III. Although they also, typically, use a ‘ball and spring’ molecular model and employ terms similar to those described for Class I, they often consist of highly specialized or very limited functional forms. A number of them are based on Urey–Bradley or Buckingham formalisms, sometimes with slight modifications or mixtures of functional form. They might also be intended for limited application, for example, the Goebel et al. FF⁷⁴ designed to treat maltose and amylose in the solid phase and whose functional form includes only van der Waals, charge and hydrogen-bonding interactions. Although FFs such as these might be very successful when applied to appropriate situations, they should only be applied to other situations after stringent validation.

DEVELOPMENT AND VALIDATION OF PARAMETERS

The methods used to develop and validate the parameters are at least as important as the functional forms. It is for this reason that the term ‘force field’ typically refers to the functional form and its parameters. Parameters are often developed with a certain philosophy in mind, and the proper addition of new parameters to an FF requires adherence to strict protocols for their generation. For example, the GLY-CAM family of FFs employs a paradigm in which the smallest chemical moiety required to model a chemical context is used as the basis for torsion terms and charge generation. In the case of exo-anomeric torsion terms, minimal models extending up to tetrahydropyran structures are employed. For charges, however, an entire monosaccharide must be used as the simplest unit. The charges themselves are developed using a relatively simple QM method, modified¹²¹ so that the charges result in accurate simulations of monosaccharide crystals, but many solution-phase conformations must be properly sampled and their charges averaged.

Sidebar Equation 1

$$V = D_e \{1 - \exp(-a(R - R_{eq}))\}^2$$

The functional form of the Morse potential. D_e is the bond dissociation energy, R is the internuclear separation for the bonded atoms (R_{eq} at equilibrium), and a is related to the fundamental vibration frequency and D_e .

Because the development of an FF is very labor intensive, many FFs build on existing parameter sets. These relationships are noted in Tables 1 and 2. The parameters might originate from any number of sources: spectroscopy, crystallography, etc. When there are no appropriate experimental values, QM methods are often used. Sometimes, even if the parameter was initially inspired by experiment, its value is changed slightly until some bulk property is reproduced in simulation. This latter is especially challenging for carbohydrates as there is often little usable information regarding their bulk properties.

Bond and Angle Parameters

The overwhelming majority of bond and angle equilibrium values are determined by adjusting the parameters until MD simulations reproduce X-ray crystallographic data (Table 2). In general, the data come from high-resolution studies of small-molecule crystals. Collections of these data are available, one of the more popular being the Cambridge Structural Database.¹²² Force constants generally come from infrared spectroscopic data or QM calculations. In the latter case, the lowest energy points for QM-derived force versus angle or bond curve are fit to a harmonic potential from which the force constant is extracted. In the Class II FFs, of course, QM methods would be fit to an anharmonic potential, for example a Morse-like potential (see Ref 123, p. 133). When they are taken from experimental values, the data are sometimes used without modification. Of course, a number of FFs do not consider bonds and angles as modifiable units at all.

Torsions

As mentioned above, torsion terms are most commonly derived from QM calculations. Note that they are not fit directly to the QM calculations, but to the difference between the QM and MM energies. That is, they serve merely as a correction to the MM energy that would be calculated in absence of the torsion term. For these, potential energy versus dihedral angle curves are generated and then fit to a cosine expansion, for example, the third summation in Eq. (2). In some cases, the parameters are further modified until simulations reproduce experimental observations. For biomolecular FFs, the cosine is generally expanded up to three terms to accommodate torsions typically encountered from linear through tetrahedral atomic electronic geometries. A number of the FFs also employ improper torsion terms for geometries that are difficult to maintain otherwise, for example, planarity requirements associated with double bonds.

Treatments of the Anomeric and Exo-Anomeric Effects—As the anomeric and exo-anomeric effects are the sort of electronic subtleties for which torsion terms are designed, a number of FFs do not employ special functionality to describe them. However, they all treat them in some manner (see Figure 6 and Table 2). In the more recent GLYCAM FFs, for example, they are treated via the cumulative effect of terms relevant to the anomeric center and linkages. The assignment of a glycan-carbon atom type, used for all carbons in a monosaccharide, along with monosaccharide-specific charges, allows these critical torsions to be modeled without the need to deviate from the standard functional form or to assign special types to anomeric atoms.

Atomic Charges

The electronic interactions that give rise to the anomeric effect and the exo-anomeric effect also result in complex charge distributions within oligosaccharide monomers. The large number of polar bonds in close proximity is sufficient, alone, to generate complex charge landscapes. When these are constrained to a ring and each possesses significant off-axis regions of ESP, the complexity increases significantly. Although most atomic partial charges in modern FFs are fit to QM electrostatic potentials, a few employ other methods. For example,^{31–35} the latest CHARMM FFs (Table 2) adjust initial QM charges until

simulations of pure substances or simple mixtures reproduce quantum mechanically derived solute-water energies and distances. The charges are refined further until simulations reproduce bulk properties for neat liquids. For those employing purely QM methods, the trend has been toward assignment of charges using restrained ESP (RESP),¹²¹ which is a modification of charges derived from the gas-phase ESP such that bond polarities are dampened.

Atomic Sizes

Molecular mechanics FFs treat atoms as spheres the sizes of which are described by hard or soft potential functions. With a hard potential, the spheres have sharply defined, impenetrable surfaces. Soft potentials define the spheres as a mixture of attractions [e.g., first term, last summation in Eq. (2)] and repulsions (next term) between any two atoms. In these, the equilibrium distance between any two atoms is the potential energy minimum. At shorter distances, the two atoms experience increasingly strong mutual repulsion. At longer distances, they experience progressively weaker attraction. Most treatments of atomic sizes are based on soft potentials. Only a few CarbFFs employ hard sphere treatments. The majority of soft-sphere models are Lennard-Jones potentials [first two terms, last summation in Eq. (2)]. A few are based on Buckingham's formalism. Parameters for the potential functions come primarily from thermodynamic data, bulk properties such as density and crystal packing, and quantum calculations. Early FFs relied heavily on fitting these parameters to crystal packing and lattice energy while those developed since the mid-1990s have primarily focused on reproducing liquid simulation properties such as density, heat of vaporization, and solvation free energy (Table 2).

Validation of Parameters

It can be difficult to separate parameter development from validation since the parameters are often developed so that they reproduce experimental data. However, the processes are sometimes distinct. That is, when practical, researchers might divide target molecules into a parameterization set used to develop and refine FF parameters, and a testing set used to show that the parameters are capable of reproducing other, relevant models. Alternately, they might parameterize based on one set of experimental data and validate based on a different set. For many carbohydrates, for example, poly- and oligosaccharides, appropriate experimental data can be difficult to obtain, and CarbFF developers often must validate against data that might not be an obvious choice. The challenge in these cases is to find experimental data corresponding to a characteristic that can be calculated from the results of an MD simulation. For example, they might validate against well-characterized vibrational spectra (i.e., IR, Raman, etc.) for smaller moieties. Torsional potentials, charges, and van der Waals are often validated by comparing energy differences between isomers and anomers. As mentioned in the introduction, CarbFFs are often validated indirectly by predicting ensembles of structures and, from them, calculating NMR properties such as J-couplings. No single validation method is sufficient to confirm the success of any FF, and the methods chosen often depend on the intended application of the FF.

A SURVEY OF RECENT APPLICATIONS

To gain insight into the current uses of classical FFs to study carbohydrates, the literature from January, 2009, to April, 2010, was surveyed. See the Supplementary Information for details regarding how the survey was conducted. Notably, the survey was designed to gain an overview of all uses of classical FFs to model carbohydrates during that period, not merely the CarbFFs. To that end, rather than search on specific methods, FFs or citations, the survey employed very general search terms. The initial search returned many articles, and only those relevant to the survey are considered here. Although this survey is not comprehensive, it should be representative.

The procedure yielded 99 papers^{124–222} in which a classical FF, which was not necessarily a CarbFF, was applied to a carbohydrate. Studies that considered only DNA or RNA were excluded. The 99 papers were then classified according to FF used, type of calculation and system studied among others. As it would be impractical to assess 99 articles individually here, trends will be noted, with specific articles given as examples. Interested readers will find an annotated bibliography of the articles in Tables 3 and 4. Again, references will only be explicitly given where statements reflect specific articles.

Trends and Anecdotes

The first notable but unsurprising statistic is that the FFs were used primarily in studies of biological relevance (Figure 7). Here, a study was classified as biologically relevant only when it targeted a specific biological system or process. For example, calculations¹⁸² performed to assess the biological relevance of conformational ensembles derived from solution was not considered a biological application despite that the study's inspiration is biological. Instead, it was classified as a study of carbohydrates as chemical substances. However, another study¹²⁸ that considered the effect of sulfation on the conformations of a small set of galactobiosides was considered biologically relevant because the study considered a lack of cross-reactivity within a specific pathway found in two varieties of sea urchin. Of the 63 studies classified as biologically relevant, all but two were inspired by carbohydrate–protein interactions of some sort, and 48 involved direct simulation of a carbohydrate–protein interaction. The remaining two concerned themselves with lipid bilayers: the effect of trehalose on drying¹³⁰ and the high rate of ribose permeation compared to similar glycans.¹⁴⁸

Given the rapidly growing interest in alternative fuels and 'green' processes in general, it was surprising to find only five studies concerned with a specific technological application. Again, this definition is strict: for example, an otherwise biological study that was inspired by interest in biofuels was classified as biological. Only studies involving a specific technological application were classed as technological. One¹³⁷ presented a simulation of an enzymatic biofuel cell. Another¹³⁸ sought ways to improve pigmentation in foods. The other three studied solvated glucose in silica nanochannels,¹⁵³ the elastic properties of nanomaterials with intercalated alginate,²¹¹ and the self-assembly of alginic acid around a carbon nanotube.¹⁵²

Of the physical and chemical properties studies, about half were devoted specifically to conformational properties. Given the importance of carbohydrate conformation, this is reasonable. However, despite earlier suggestions regarding the influence of NMR on the development of CarbFFs, only about a third of these studies compared to NMR values. Of those, about half used the calculations to assist in the interpretation of NMR data rather than as a validation of the calculation. One study¹³⁹ turned this around, using NMR experimental data to help interpret the computational results. These substance-directed applications varied more than the biologically relevant ones. Among others, there are studies targeting phase transitions,^{140,141} Raman and IR activity,^{214,221} gel formation,¹⁷⁵ spontaneous organizations,²²² and behaviors of cellulose polymers when pulled upon by the probe tip in an atomic force microscope.¹⁸¹

Another notable trend is in the number of studies, 42 in this survey, that are using the calculations as a data analysis tool within a concurrent experimental context. That is, rather than doing the calculation for its own sake and comparing results to other experimental or computational data, these studies (Code 'A' in Table 4), employed simulations as a means of interpreting experimental data reported within the same article. That researchers are doing this with success, speaks well of the maturity of CarbFFs. Of particular interest in that regard are the studies^{136,186,193,203} that used a simulation to help guide their experimental design.

In 66 of the studies, researchers used their calculations to make some sort of commentary (Code 'C' in Table 4) on an experimental or computational observation, whether existing or proposed. The other 33 studies concerned method validations or they used the calculations in some other manner, for example, to facilitate NMR data analysis. The number of studies making comments implies confidence with use of the FFs. However, only 26 of them (39%) provided validation of their computational method against experiment. Another 22 (33%) cite external sources for validations, but 18 (27%) appear to have performed their calculations without any. When all 99 studies are considered, the validation numbers remain proportional: 41, 27, and 31.

To be classified here as having validated against experiment, three conditions must be met. First, the authors must compare computational results to equivalent experimental, or in a few cases computational, results. Comparisons to other calculations are acceptable only when appropriate, for example, when a study proposes a new algorithm and agreement with established methods must be shown. Next, their comparison must support their choice of methodology rather than show only shortcomings. Finally, the validating comparison must be independent of other conclusions drawn from the calculation (see section *Validation*). Whether classified as validating against experiment or via citation, no judgment is made here regarding the appropriateness of the comparison or citation: the classification represents only the authors' report.

Direct Comparisons of Carbohydrate Force Fields

Two articles from the search performed comparisons between FFs. Only one of those had as a goal to determine the best FF for a task. That one¹⁹⁹ studied the ability of current FFs in MD simulation to reproduce ring puckering in 2-O-sulfo- α -L-iduronic acid. This is a

challenging system to study in that iduronic acid, unlike many other monosaccharides, transitions between different ring forms at ambient conditions. They compared GROMOS96 (GRO-MACS 3.3) to a nonstandard modification of GLY-CAM06 and found that GROMOS96 better predicted NMR observables. The authors of the other study¹⁹⁷ sought to maximize the possibility of interpreting their NMR data. To that end, they employed multiple methods, each with an associated FF, for calculating torsion angles and energies. They found that the methods were consistent with each other and the NMR data, but they were unable to confirm the presence in solution of several high-energy conformations. The other two studies^{196,198} that employed multiple FFs did not compare them but rather used them for different computational aspects of their studies.

RECOMMENDATIONS FOR STUDIES EMPLOYING CARBOHYDRATE FORCE FIELDS

Choosing a Force Field

An FF should be chosen based on the applications, types of system and environmental conditions for which it was designed. For example, the MM3⁸⁷ FF has been applied extensively to carbohydrate systems in the gas phase for reproducing low-energy QM conformers and potential energy curves; however, it may be an inappropriate choice for solution phase dynamics because it was not parameterized or developed to run accurately or efficiently in explicit solvent. Similarly, an FF designed for reproducing IR and Raman spectroscopy, such as SPASIBA,⁷⁰ may be a poor choice for studying solvated carbohydrate dynamics. On the other hand, AMBER,²¹ CHARMM,³⁴ GLYCAM,⁵¹ and GROMOS⁵⁹ FFs are validated for solvated systems, but might not reproduce crystal-phase infrared data as well as some others.

As each CarbFF might have been designed for a different purpose, the chemical systems for which it was intended should also be considered. For example, FF3³⁷ was designed for comparing relative energies of α - and β -D-glucopyranose and might not be useful in any context beyond that. Even where carbohydrates were included during parameterization, the FF might not treat subtle interactions. For example, in the case of the DREIDING FF,⁸³ the anomeric effect was not considered during development. Although it is possible that CarbFFs such as these could be successfully applied in certain simulations, it should not be done without rigorous validation. Even the generalized CarbFFs should be used with caution when they are applied to classes not considered during development. It is also important to note that the generalized CarbFFs represent a larger set of carbohydrate classes well by equally distributing errors, reducing specific accuracy to improve overall applicability.

Studies Involving Noncarbohydrates

Carbohydrate simulations often involve noncarbohydrate structures, for example, proteins, membranes, carbon nanotubes, etc. In these cases, it might be necessary to use more than one FF within the simulation. When mixing FFs, it is important to understand and account for differences in the proper implementation of each FF. Many aspects of proper FF usage are beyond the scope of this review, but they are important. For example, some FFs employ special scaling of charge–charge or van der Waals interactions within a molecule,

particularly for atoms separated by three bonds (called 1–4 scaling), four bonds (1–5 scaling) or five (1–6 scaling). That is, nonbonded interactions between two atoms are often scaled when they are both part of the same molecule and are separated by two, three, or four bonded atoms. Of course, not all FFs do so in the same manner, and some do not scale at all. When FFs that employ different scaling factors are used in conjunction with each other, proper treatment of these differences can be critical.

Many software packages only allow the use of certain FFs in limited combinations. However, some of the more flexible packages provide mechanisms by which researchers can change or mix FF parameters. When it is possible to import multiple FFs or change parameters, it becomes the duty of the researcher to ensure that all FF components are treated properly and that they are appropriate to the intended simulation. Ensuring proper treatment can be challenging because differences in implementation might be written into the software code.

Mixing and Changing Parameters within a Force Field

To develop an FF completely *de novo* can be prohibitively labor intensive. For this reason, and to avoid needless duplication of effort, almost all FFs rely to some extent on parameterizations from other studies. When the need arises, therefore, it is appropriate to extend an FF, for example, to treat unusual carbohydrate moieties. A few examples^{193–195,199} of modified CarbFFs have been considered here. The most common modification is the generation of atomic charges for novel, FF-appropriate residues. Because all FF parameters are interdependent, any one necessarily affects the behavior of all the others. For this reason, FF extensions should be made in a manner consistent with the original FF-generation protocols and should be well validated before use.

Nonstandard Conditions

As mentioned earlier, most FFs, including CarbFFs, are designed to behave well for nonreactive systems at or near standard ambient conditions. The treatment of reactions is currently beyond any known CarbFFs. Methodologies exist, such as the empirical valence bond (EVB)²²³ facility in the AMBER molecular modeling suite, but researchers must supply parameters appropriate to the system of interest. There are two issues regarding deviation from standard ambient conditions. First, reactions might occur more frequently in an experimental situation, but they are not modeled by the simulation. This can, at times, be an advantage, for example, when using simulated annealing to increase conformer sampling. It should be noted, however, that for monosaccharides, it might be necessary to apply restraints to prevent ring conformer changes during simulated annealing. The other problem is that if the CarbFF (or any FF) was not developed for the conditions, it likely will not model them well. In these cases, as with the altered FF, it is especially important that the researcher perform validations.

Validation

In the case of any classical FF, validation on one chemical moiety does not necessarily transfer to another. This is especially true with carbohydrates, whose intricate electronic structures make generic parameterization difficult. Consider the sulfated iduronic acid study

mentioned above. Existing CarbFFs have modeled many monosaccharides well, including ring geometries for some challenging monosaccharides, for example, sialic acid.²²⁴ However, in the case of sulfated iduronic acid, development outside of the scope of the original parameterization did not lead to optimal performance.

Validation of an FF is often not trivial, but it is necessary. The validation method should be different from the parameterization process whenever possible. It should also compare properties relevant to the simulation, but that are not targeted in the computational analysis. For example, consider a study concerning the effect of oligosaccharide branching on diffusion rates. A reasonable validation might include comparisons, using chemically relevant systems, to known diffusion rates and NMR-derived conformational data. This establishes that the method properly mimics diffusion rates and structural properties, making it reasonable to draw conclusions regarding relationships between the two.

Reporting Computational Procedures

In a significant number of the surveyed articles, additional methodological details would be required before the studies could be reproduced. In 18 of the articles, it was not possible to determine precisely which FF was being used. Even when the FF could be determined, it was often difficult to do so or it was difficult to determine precisely how the FF was used. The 'Force Field Notes' in Table 4 contain further information.

Certain pieces of information are always required for reproducing computational results. First, sources of all input data must be divulged, for example, the origins of initial coordinates and the identities of parameter sets. Next, relevant details regarding the computational methods must be described. In addition to identifying the overall method (e.g., MD), these should also include run-control information such as simulation length, time step, boundary conditions, temperature, alternate functional forms, etc. Finally, the origin of the software should be identified, even if the software was written by the researchers. When referencing publicly available software, the publisher, source, version number, and year should be included. Of course, in some situations, additional information might be required, especially when multiple methods or FFs are employed, but this minimum set is essential. Researchers should also reference adequately. For example, the FF and the simulation software are typically two distinct references. In almost all cases, the software manual is not an appropriate reference for any aspect of a simulation method. Software manuals typically contain the relevant references.

It is also highly recommended that researchers validate their choice of computational method. In cases where the researchers are closely following previously validated procedures, a citation might be sufficient. However, when any part of the procedure or system studied is novel, validation against experiment is the better choice (see sections *Trends and Anecdotes* and *Validation*). In any case, the validation method should be clearly identified as such. The *Methods* or *Experimental* section is the most obvious location for validation information, but many authors place the information at the beginning of the *Results* section.

FUTURE DIRECTIONS

Although there will always be a place for well-constructed Class I FFs, the proper modeling of the more critical nuances of carbohydrate interactions will require Class II or III treatment. For example, a Class I FF, and even most Class II FFs, will never be able to treat properly anomeric inversion. Classical FFs, in general, have difficulty treating effects due to conformational change, such as charge alteration during ring inversions. They also have difficulty modeling finer interactions such as those involved with monosaccharide-tryptophan stacking. These effects, and others like them, are of great importance in the understanding of many of the subtler interactions involving carbohydrates. On the other hand, such an increase in complexity comes with great cost, making simulations of very large systems impractical. For this reason, whenever practical, the opposite direction must also be pursued. That is, united atom approaches and coarse-grained models must be made general and easily adapted to new computational situations.

CONCLUSION

After a few decades of evolution, a number of CarbFFs are available and widely used. However, a large number of researchers still employ FFs that were not developed for carbohydrates in their models. That CarbFFs are used by researchers whose primary expertise is not computational indicates a pleasing level of maturity in the field. However, in almost all contexts improvements need to be made in how the use of CarbFFs is reported in the professional literature. It is up to the community, including reviewers and software producers, to ensure that published articles observe standard reporting practices. Overall, CarbFFs appear to be approaching a limit in terms of what is possible within the traditional Class I formalism, and they need to expand into other computational contexts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Fraction of reviewed force fields, per decade ending with 2010, employing quantum mechanical (QM) methodologies in the development of atomistic charges (blue) and torsion parameters (red). In the first decade, only two CarbFFs were published, and neither used any QM methods.

FIGURE 2.

Fraction of reviewed force fields, per decade, for which nuclear magnetic resonance [NMR (red)] and crystallographic data (blue) were used as experimental validation. The reversal of trends in the 1980s almost certainly reflects advances in computing and NMR.

FIGURE 3.

Number of carbohydrate force fields (CarbFFs), per decade, categorized by the overall system to which the design was targeted. Some CarbFFs (red) were designed to treat small subsets of carbohydrates by modeling only specific anomers, saccharides or linkages. Others were designed to treat a more general set of carbohydrates within a biological context (green) or as organic molecules (blue).

FIGURE 4.
Number of carbohydrate force fields, per decade, by classification.

FIGURE 5. Number of carbohydrate force fields, per decade, classified according to the number of energetic components in their functional form.

FIGURE 6. There is a distinct lack of trend in carbohydrate force field treatment of the anomeric effect.

FIGURE 7.
Force field use by application class and force field category.

TABLE 1

The Historical Development of Force Fields whose Development Addressed Carbohydrates

References	Force Field Family	Version Name, Year First Published	Number of Citations as of 10/18/2010 ²²⁶	Applicable Molecular Classes	Developed Simulation State(s)	Emphasized Experimental Data Reproduction	Anomeric Treatment	Exo-Anomeric Development Molecule(s)
14	AMBER	Edge et al., 1990	75	Man- α -1,2-Man- α -OH, proteins and nucleic acids	GP, Esolv	X, NMR, RE	Single anomer	Man- α -1,2-Man- α -OH
15	AMBER	Homans et al., 1990	354	Carbohydrates (modifications to a biomolecular FF)	SP, Esolv	X, NMR, RE	Atom types	Dimethoxymethane
16, 17	AMBER	Zheng/Glennon et al., 1992	31, 92	Carbohydrates (modifications to a biomolecular FF)	Esolv	X, NMR, RE	Charges	THP-derivatives
18	AMBER	UA-AMBER *, 1996	80	Carbohydrates (modifications to a biomolecular FF)	GP, Isolv	NMR, RE	Charges	Small molecules
19	AMBER	AA-AMBER *, 1997	50	Carbohydrates (modifications to a biomolecular FF)	GP, Isolv	NMR, RE	Charges	THP-derivatives
20	AMBER	AMB99C, 2000	45	Carbohydrates (modifications to a biomolecular FF)	GP, SP	X, Gas, RE	Atom types	THP-derivatives
21	AMBER	AMB06C, 2009	0	Carbohydrates (modifications to a biomolecular FF)	SP, Esolv	X, NMR, RE, PT	Atom types	THP-derivatives
22	CCEM	Mukhopadhyay and Rao, 1988	5	β -L-arabinose	SP	X, RE	Anomer-dependent functions	Monosaccharides
23	CCEM	Rao et al., 1989	11	Monosaccharides	SP	X, RE	Anomer-dependent functions	Monosaccharides
24	CHARMM	Ha et al., 1988	239	Monosaccharides (α -D-glucopyranose)	GP, AmbSolv	Vib, X		Small molecules
25	CHARMM	CHEAT, 1993	51	Carbohydrates (modifications to a biomolecular FF)	GS, Isolv	X, NMR, RE		Cyclic small molecules
26	CHARMM	CHEAT95, 1995	50	Carbohydrates (modifications to a biomolecular FF)	Isolv	NMR, RE	Atom types	Small molecules
27	CHARMM	Reiling et al., 1996	68	Carbohydrates (modifications to a biomolecular FF)	SP, Esolv	Gas, RE		Small molecules
28	CHARMM	Palma et al., 2001	9 *	Carbohydrates (modifications to a biomolecular FF)	SP, Esolv	NMR, RE		Small molecules
29	CHARMM	CSFF, 2002	134	Carbohydrates (modifications to a biomolecular FF)	Esolv	NMR, Vib, RE		Small molecules
30	CHARMM	PARM22/SU01, 2003	29	Carbohydrates (modifications to a biomolecular FF)	Esolv	NMR, RE		THP-derivatives
31, 32, 33, 227*, 34, 35	CHARMM	Guvench/Hatcher et al., 2008	16, 2, 5 and 2, 4, 0	Carbohydrates (modifications to a biomolecular FF)	GP, Sp, Esolv	X, NMR, RE, Gas, Vib		THP-derivatives, THF-derivatives, Cyclohexane-derivatives
36	CFF ^[H]	Hwang et al., 1998	73	Carbohydrates (modifications to a biomolecular FF)	GP	Gas, Vib	Coupling terms	Small molecules

References	Force Field Family	Version Name, Year First Published	Number of Citations as of 10/18/2010 ²²⁶	Applicable Molecular Classes	Developed Simulation State(s)	Emphasized Experimental Data Reproduction	Anomeric Treatment	Exo-Anomeric Development Molecule(s)
37, 38	CFF ^(RI)	FF3, 1977	39 [*] , 54	α - and β -D-Glucopyranose	SP	X, Vib, RE		Optimized sugar crystal geometries
39	CFF ^(RI)	FF300, 1978	16	α - and β -D-Glucopyranose	SP	X, Vib, RE		
40, 41	CFF ^(RI)	FF400, 1979	57, 49	Carbohydrates	SP	X, Vib, RE		Small molecules
42	CFF ^(RI)	FF301, 1982	52	α - and β -D-Glucopyranose	SP	X, Vib, RE		
42	CFF ^(RI)	FF422, 1982	52	Carbohydrates	SP	X, Vib, RE		Small molecules
43, 44	CFF ^(RI)	PEF9 IL, 1993	32, 18	Carbohydrates and lipids	SP, GP	X, Vib, RE	Atom types	Small molecules
45	CFF ^(RI)	PEF95SAC, 1997	18	Carbohydrates	SP, GP	X, Vib, RE	Atom types	Small molecules
46	GLYCAM	GLYCAM93, 1995	300	Carbohydrates (modifications to a biomolecular FF)	SP, Esolv	X, NMR, RE	Atom types and charges	THP-derivatives
47	GLYCAM	GLYCAM2000, 2001	192	Carbohydrates (modifications to a biomolecular FF)	SP, Esolv	X, NMR, RE	Atom types and charges	THP-derivatives
47, 48, 49	GLYCAM	GLYCAM04, 2001	192, 61, 48	Carbohydrates (consistent with AMBER FFs)	SP, Esolv	X, NMR, RE	Charges	THP-derivatives
50	GLYCAM	GLYCAM06EP (GLYCAM04EP), 2007	5	Carbohydrates (consistent with AMBER FFs)	SP, Esolv	X, NMR, RE	Charges	THP-derivatives
51	GLYCAM	GLYCAM06, 2008	63	Carbohydrates (consistent with AMBER FFs)	SP, Esolv	X, NMR, RE	Charges	THP-derivatives
52	GROMOS	Koehler et al., 1987	109	Carbohydrates (modifications to a biomolecular FF)	SP	X, RE	1,4-Scaling factors	Small molecules
53	GROMOS	Kouwijzer et al., 1995	24	Monosaccharides	GP, AmbSolv	X, Vib	1,4-Scaling factors	Small molecules
54	GROMOS	43A1, 1996	40	Carbohydrates (modifications to a biomolecular FF)	GP, Esolv	NMR, RE	Atom types, 1,4-Scaling factors	Methoxymethanol and dimethoxymethane
55	GROMOS	Spieser et al., 1999	31	Carbohydrates (modifications to a biomolecular FF)	GP, Esolv	NMR, RE	Atom types, 1,4-Scaling factors	Monosaccharides
56, 57	GROMOS	45A3, 2000	45 [†] , 199 [†]	Carbohydrates (modifications to a biomolecular FF)	Esolv	NMR, RE	1,4-Scaling factors	Small molecules
58	GROMOS	53A5 and 53A6, 2004	311 [†]	Biomolecular FF	Esolv	NMR, RE	1,4-Scaling factors	Not specifically addressed by authors
59	GROMOS	45A4, 2005	61	Carbohydrates (modifications to a biomolecular FF)	Esolv	NMR, RE		Hexopyranoses
60	GROMOS	56A_CARBO, 2010	0	Carbohydrates (modifications to a biomolecular FF)	Esolv	NMR, RE		Hexopyranoses
61, 62, 63	HSEA	Lemieux/Thogersen et al., 1978	258, 428, 329	Carbohydrates	Solv	NMR, RE	Anomer-dependent functions	Dimethoxymethane
64	LUCIFER	Marsden et al., 1988	9	Carbohydrates (modifications to a biomolecular FF)	Esolv	NMR, RE	Lone pairs	THP-derivatives

References	Force Field Family	Version Name, Year First Published	Number of Citations as of 10/18/2010 ²²⁶	Applicable Molecular Classes	Developed Simulation State(s)	Emphasized Experimental Data Reproduction	Anomeric Treatment	Exo-Anomeric Development Molecule(s)
65	OPLS-AA	Carbohydrates, 1997	217	Carbohydrates (modifications to a biomolecular FF)	GP, Esolv	NMR, Gas, RE	Atom types	Hexopyranoses
66	OPLS-AA	SEI, 2002	40	Carbohydrates (modifications to a biomolecular FF)	GP, Esolv	NMR, Gas, RE	1,5- and& 1,6-Scaling factors	Hexopyranoses
67, 68, 69, 70	SPASIBA	Derreumaux/Sekkal/ Dauchez et al., 1990	27, 34, 5, 12	Carbohydrates (modifications to a biomolecular FF)	SP	X, Vib		Glucopyranose disaccharides
71	SPASIBA	Durier et al., 1997	3	α -D-glucose (modifications to a biomolecular FF)	SP, GP	X, Vib	Single anomer, 1,4-Scaling factors	Small molecules
72	Tvaroška	EAE, 1984	34	Carbohydrates	SP	X, Vib, RE	Anomer-dependent functions	THP-derivatives
73	Tvaroška	PF, 1986	128	Carbohydrates	SP	X, RE		Small molecules
73	Tvaroška	NBEA, 1986	128	Carbohydrates	SP	X, RE	Anomer-dependent functions	Dimethoxymethane
73	Tvaroška	PFOS, 1986	128	Carbohydrates	SP	X, RE	Anomer-dependent functions	THP-derivatives
74		Goebel et al., 1970	91	Maltose and amylose	SP	X, RE		
75, 76		Sundararajan/Rao et al., 1968	51, 77*	Pyranose monosaccharides	Solv	NMR, RE		
77		Rao et al., 1971	54	Hexopyranoses	Solv	NMR, RE		Hexopyranoses
78		Rees and Smith, 1975	23	Carbohydrates	Solv	NMR, RE		Disaccharides
79, 80		Lipkind et al., 1984	64, 38	Monosaccharides	Solv	NMR, RE		Monosaccharides
81, 82		Sekkal-Rahal et al., 2007	1, 0	Monosaccharides	SP	X, Vib		Small molecules
83	DREIDING	Mayo et al., 1990	1870 [†]	Generic molecular FF	SP, GP	X, Gas, RE		Unknown—ambiguous crystal and QM structures
84	ESFF	Shi et al., 2003	37	Generic molecular FF	SP	X, RE	Charges	Small molecules
85	MMI	CARB, 1980	158	Carbohydrates (modifications to a generic molecular FF)	SP, GP	X	Bond and angle	
86	MM2	Norskov-Lauritsen and Allinger, 1984	86	Generic molecular FF	SP, GP	X, Gas, RE	Anomeric function	Small molecules, THP-derivatives, and other cyclic structures
87	MM3	Allinger et al., 1990	326 [‡]	Generic molecular FF	SP, GP	X, Gas, RE	Anomeric function	Small molecules, THP-derivatives, and other cyclic structures
88, 89	MM4	Allinger et al., 2003	27, 21	Generic molecular FF	SP, GP	X, Gas, RE	Anomeric function	Small molecules, THP-derivatives, and other cyclic structures
90, 91	TRIPOS	PIM, 1989	1599 [‡] , 43*	Generic molecular FF (includes metals and ions)	SP, GP	X, RE	Atom types and charges	THP-derivatives
92	TRIPOS	PIM, 1999	24*	Carbohydrates (modifications to Generic MM FF)	SP, GP	X, RE	Atom types and charges	THP-derivatives

Here, each FF is classified according to family, and within that, the force fields (FFs) are listed according to their first appearance in the literature. Generic molecular FFs are listed below those specific to carbohydrates to differentiate between them. A key for the abbreviations is provided. The Applicable Molecular Classes field describes the originally developed application for the listed FF including any relevant notes about its development as a modified FF. The Developed Simulation State(s) describes the state(s) of matter for which the FF was originally intended to model while the Emphasized Experimental Data Reproduction is the type of experimental data for which the FF was intended to reproduce [as could be best determined from the original publication(s)]. The Anomeric Treatment is a description of how

different anomers (α - and β -) for the same saccharide are particularly treated by the FF—blank indicates no special treatment. The Exo-Anomeric Development Molecule(s) column describes the molecules used in parameterizing the exo-anomeric effect. In the case of monosaccharides and THP-derivatives, an O-Methyl group is used to represent the exo-anomeric torsion while the term ‘Hexopyranoses’ is used to describe the use of multiple models for hexopyranose monosaccharides and THP-derivatives with O-Methyl for the exo-anomeric group as well as hexopyranose dissacharides with ψ -torsions. It should be noted that the ‘GLYCAM’ family is actually a part of the AMBER simulation package; however, the FF parameters for GLYCAM04, GLYCAM06EP (also called GLYCAM04EP) and GLYCAM06 are independent from, though consistent with, other AMBER biomolecular FFs except with respect to the treatment of 1,4-scaling factors. Prior to the release of AMBER11 simulation package,²²⁵ AMBER did not allow separate 1,4-scaling values when mixing force fields. In applications when mixing AMBER and GLYCAM FFs, it was found to be reasonable to use the AMBER scaling factors for both force fields.⁴⁷

Developed simulation state(s): GP, gas phase simulations; SP, solid phase simulations; Esolv, explicit solvated simulations; Isolv, implicit solvated simulations (must use a parameterized implicit solvent model, not simply a high dielectric); Solv, solution simulation properties without a parameterized solvent model (typically using a high dielectric); AmbSolv, ambiguous solvation state simulations.

Emphasized Experimental Data Reproduction: X, crystallographic structural data reproduction; NMR, solution NMR structural data reproduction; Gas, gas phase structural data reproduction; PT, phase transition structural reproduction; RE, relative energies of isoforms in developed application states; Vib, vibrational properties.

Anomeric Treatment: Single anomer, FF developed for a single anomer or sugar; Atom types, different atom types for different anomers; Charges, different charges for different anomers; Scaling factors, different scaling factors used to describe the anomeric effect; Bond and Angle, different bond and angle terms used to describe different anomers; Anomeric function, special function to describe the anomeric effect; Anomer-dependent functions, different function(s) for each anomer; Coupling terms, special coupling terms used to describe the anomeric effect; Lone pairs, lone pairs are used to describe the anomeric effect.

* Indicates use of Google Scholar²²⁸ (<http://scholar.google.com>) to obtain the number of citations because the reference is a book.

** Indicates article was retracted. This reference was included to show the correct citation.

[†] Indicates that the reference is for a generic or nonspecific biomolecular FF which means the reference count includes an unspecified number of noncarbohydrate simulation references.

Details Regarding the Energetic Components of the Functional Forms and the Parameter Development Methods for the Force Fields in Table 1

References	Force Field Family	Version Name, Year first published	vdW		Bonds		Angles		Torsions		H-Bond	Other
			Equation Type	Data Fit To	Equation Type	Data Fit To	Equation Type	Data Fit To	Equation Type	Data Fit To		
14	AMBER	Edge et al., 1990	12-6LJ	X	HB	X, Vib	HA	X, Vib	T, IT	Vib, NMR, QM	M	
15	AMBER	Homans et al., 1990	12-6LJ	X	HB	X, Vib	HA	X, Vib	T, IT	X, QM	QMamb	$\alpha\beta$
16, 17	AMBER	Zheng/Glennon et al., 1992	12-6LJ	X	HB	X, Vib	HA	X, Vib	T, IT	X, Vib, NMR, QM	ESP	12-10HB
18	AMBER	UA-AMBER*, 1996	12-6LJ	X	HB	X, Vib	HA	X, Vib	T, IT	QM	ESP	12-10HB
19	AMBER	AA-AMBER*, 1997	12-6LJ	X	HB	X, Vib	HA	X, Vib	T, IT	QM	ESP	12-10HB
20	AMBER	AMB99C, 2000	12-6LJ	X	HB	X, Vib	HA	X, Vib	T, IT	QM	ESP	$\alpha\beta$
21	AMBER	AMB06C, 2009	12-6LJ	X	HB	X, Vib	HA	X, Vib	T, IT	QM	ESP	$\alpha\beta$
22	CCEM	Mukhopadhyay and Rao, 1988	12-6LJ	X					T, Tano	QM, Hyb	MO-LCAO	12-10HB
23	CCEM	Rao et al., 1989	12-6LJ	X					T, Tano	QM, eBH	MO-LCAO	12-10HB
24	CHARMM	Ha et al., 1988	12-6LJ	X	HB	X, Vib	HA	X, Vib	T, IT	X, Vib	QMamb	
25	CHARMM	CHEAT, 1993	12-6LJ	X, eBH	HB	X, Vib	HA	X, Vib	T, IT	X, Vib, eBH	SIE	12-10HB
26	CHARMM	CHEAT95, 1995	12-6LJ	X	HB	X, Vib	HA	X, Vib	T, IT	eBH	SIE	12-10HB
27	CHARMM	Reiling et al., 1996	12-6LJ	X	HB	X, Vib	HA	X, Vib	T, IT	QM	SIE	12-10HB, (6-4HB)
28	CHARMM	Palma et al., 2001	12-6LJ	Den, Vap, X	HB	ED, X, QM, Vib	HA	ED, X, QM, Vib	T, IT	Vib, QM	SIE	12-10HB
29	CHARMM	CSFF, 2002	12-6LJ	Den, Vap, X	HB	Vib	HA	ED, X, QM, Vib	T, IT	NMR	SIE	12-10HB
30	CHARMM	PARM22/SU01, 2003	12-6LJ	X	HB	X, Vib	HA	X, Vib	T, IT	QM	SIE	U-B
31, 32, 33 227 **, 34, 35	CHARMM	Guvench/Hatcher et al., 2008	12-6LJ	Vap, Den, Vol, X	HB	X, Vib, QM	HA	X, Vib, QM	T	X, QM, NMR	SIE	U-B
36	$CFP^{[1]}$	Hwang et al., 1998	9-6LJ	X	AB	X, QM	AA	X, QM	T	QM	CS	ETC
37, 38	$CFP^{[2]}$	FF3, 1977	BP	X	HB	X	HA	X	T	X		
39	$CFP^{[2]}$	FF300, 1978	BP	X	HB	X	HA	X				
40, 41	$CFP^{[2]}$	FF400, 1979	12-6LJ	X	HB	X, Vib	HA	X, Vib	T	X, Vib	M	
42	$CFP^{[2]}$	FF301, 1982	12-6LJ	X	HB	X	HA	X				
42	$CFP^{[2]}$	FF422, 1982	12-6LJ	X	HB	X, Vib	HA	X, Vib	T	X, Vib	M	
43, 44	$CFP^{[2]}$	PEF91L, 1993	12-6LJ	X	AB	X, Vib	HA	X, Vib	T	X, Vib	M	$\alpha\beta$

References	Force Field Family	Version Name, Year <i>first published</i>	vdW		Bonds		Angles		Torsions		Charges	H-Bond	Other
			Equation Type	Data Fit To	Equation Type	Data Fit To	Equation Type	Data Fit To	Equation Type	Data Fit To			
45	<i>CFr^{fr}</i>	PEF95SAC, 1997	12-6LJ	X	AB	X, Vib	HA	X, Vib	T	X, Vib	M		<i>aβ</i>
46	GLYCAM	GLYCAM93, 1995	12-6LJ	X	HB	X, Vib	HA	X, Vib	T, IT	QM	ESP		<i>aβ</i>
47	GLYCAM	GLYCAM2000, 2001	12-6LJ	Vap, Den	HB	X, QM	HA	X, QM	T, IT	QM	ESP		<i>aβ</i>
47, 48, 49	GLYCAM	GLYCAM04, 2001	12-6LJ	Vap, Den	HB	X, QM	HA	X, QM	T, IT	QM	RESP		LP
50	GLYCAM	GLYCAM06EP (GLYCAM04EP), 2007	12-6LJ	Vap, Den	HB	X, QM	HA	X, QM	T, IT	QM	RESP		LP
51	GLYCAM	GLYCAM06, 2008	12-6LJ	Vap, Den	HB	X, Vib, QM	HA	X, Vib, QM	T, IT	QM, NMR	RESP		UA
52	GROMOS	Koehler et al., 1987	12-6LJ	X, Unk	HB	X, Vib	HA	X, Vib	T, IT	Unk	Unk		UA
53	GROMOS	Kouwijzer et al., 1995	12-6LJ	X	HB	X, Vib	HA	X, Vib	T, IT	Unk, X, Vib	CS		UA
54	GROMOS	43A1, 1996	12-6LJ	X, Unk	HB	X, Vib	HA	X, Vib	T, IT	QM	Unk		UA
55	GROMOS	Spieser et al., 1999	12-6LJ	X, Unk	HB	X, Vib	HA	X, Vib	T, IT	Unk, NMR	Unk		<i>aβ</i> , UA
56, 57	GROMOS	45A3, 2000	12-6LJ	Den, Vap	HB	X, Vib	HA	X, Vib	T, IT	QM, eBH	Unk		UA
58	GROMOS	53A5 and 53A6, 2004	12-6LJ	Den, Vap	HB	X, Vib	HA	X, Vib	T, IT	QM	RESP (SEI for noncarbohydrates)		UA
59	GROMOS	45A4, 2005	12-6LJ	Den, Vap	HB	X, Vib	HA	X, Vib	T, IT	QM	RESP		UA
60	GROMOS	56A_CARBO, 2010	12-6LJ	Den, Vap	HB	X, Vib	HA	X, Vib	T, IT	QM	RESP		UA
61, 62, 63	HSEA	Lemieux/Thøgersen et al., 1978	HS	X					Tano	QM			LP
64	LUCIFER	Marsden et al., 1988	9-6LJ	QM, X, NMR					T	QM	QD		Aβ
65	OPLS-AA	Carbohydrates, 1997	12-6LJ	Den, Vap	HB	X, Vib	HA	X, Vib	T, IT	QM	SIE		
66	OPLS-AA	SEI, 2002	12-6LJ	Den, Vap	HB	X, Vib	HA	X, Vib	T, IT	QM	SIE		
67, 68, 69, 70	SPASIBA	Derreumaux/Sekkal/ Dauchez et al., 1990	BP	X, Vib	HB	X, Vib	HA	X, Vib	T	X, Vib	AM1	12-10HB	U-B, ETC
71	SPASIBA	Durier et al., 1997	12-6LJ	Den, Vap	HB	X, Vib	HA	X, Vib	T	QM, X, Vib	ESP	12-10HB	U-B, ETC
72	Tvaroška	EAE, 1984							Tano	QM			
73	Tvaroška	PF, 1986	12-6LJ	X					T	Hyb			
73	Tvaroška	NBEA, 1986	12-6LJ	X					Tano	QM			
73	Tvaroška	PFOS, 1986	12-6LJ	X					T, Tano	QM, Hyb			
74		Goebel et al., 1970	BP	X							ED	12-6HB	
75, 76		Sundararajan/Rao et al., 1968	KF	X									
77		Rao et al., 1971	KF	X			HA	X			MO-LCAO		
78		Rees and Smith, 1975	9-6LJ	X					T	X	MO-LCAO		
79, 80		Lipkind et al., 1984	12-6LJ	X					T	NMR	MO-LCAO	mpHB	

References	Force Field Family	Version Name, Year <i>first published</i>	vdW			Bonds		Angles		Torsions		Charges	H-Bond	Other
			Equation Type	Data Fit To	Equation Type	Equation Type	Data Fit To	Equation Type	Data Fit To	Equation Type	Data Fit To			
81, 82		Sekkal-Rahal et al., 2007	BP	X	HB	HB	Vib	HA	Vib	T	Vib	ESP	ubsHB	U-B, ETC
83	DREIDING	Mayo et al., 1990	12-6LJ (BP)	X	HB, (AB)	HB, (AB)	Hyb	HA	Hyb	T, IT	Hyb	GC	12-10HB	
84	ESFF	Shi et al., 2003	9-6LJ	QM, X	AB	AB	QM, X, Vib	AA	QM, X, Vib	T, IT	QM, X	ENE		
85	MM1	CARB, 1980	BP	X, Vib	HB	HB	X, Vib	HA	X, Vib	T, IT	X, Vib			ETC
86	MM2	Norskov-Lauritsen and Allinger, 1984	BP	X, Vib	AB	AB	X, Vib	AA	X, Vib	T, IT	X, Vib			(LP), ETC
87	MM3	Allinger et al., 1990	BP	X, Vib	AB	AB	X, Vib	AA	X, Vib	T, IT	QM			ETC
88,89	MM4	Allinger et al., 2003	BP	X, Vib	AB	AB	X, Vib	AA	X, Vib	T, IT	QM			ETC
90, 91	TRIPOS	PIM, 1989	12-6LJ	X	HB	HB	X, Vib	HA	X, Vib	T, IT	QM	MNDO		$\alpha\beta$
92	TRIPOS	PIM, 1999	12-6LJ	X	HB	HB	X	HA	X	T, IT	QM	MNDO		$\alpha\beta$

The van der Waals (vdW), Bonds, Angles, and Torsions descriptions are divided into a simplified description of the implemented functional form (Equation Type) and the types of data used to develop the parameters (Data Fit To). The charge development method is described in the Charges section. A brief description of hydrogen bond functions (H-Bond) and unique properties of FFs (Other) are also included. A key for the abbreviations is available at the bottom of the table. In order to generate a more comprehensible table, many of the terms used here represent a simplified interpretation, and they should be taken only as a convenient guide to the literature. Values in parenthesis indicate alternately developed functions in the same force field. For example, the CHARMM Reiling et al., 1996 FF was also developed using the same protocols for a United Atom (UA) version of the same force field as well as having options for 12-10 (12-10HB) or 6-4 hydrogen bond (6-4HB) terms.

*** Indicates article was retracted. This reference was included to show the correct citation.

van der Waals (vdW): 12-6LJ, 12-6 Lennard-Jones; HS, hard sphere; 3LJ, 3-term repulsive Lennard-Jones; 9-LJ, 9-6 Lennard Jones; BP, Buckingham-Type potentials; KF, Kitaigorodsky function.

Bonds: AB, anharmonic bond potential; HB, harmonic bond potential.

Angles: AA, anharmonic angle potential; HA, harmonic angle potential.

Torsions: T, through-bond torsions, IT, improper torsions (may have very different functional forms); Tano, special ano- and/or exo-anomeric torsion function.

Types of Fitting Data (Data Fit To): X, crystallographic data (X-ray, neutron); Vib, vibrational spectroscopic techniques (IR, Raman, MW, etc.); NMR, nuclear magnetic resonance data; ED, electron diffraction; QM, quantum mechanics (includes density functional methods); Hyb, standard hybridization based barrier assignment; eBH, miscellaneous experimental techniques for barrier heights or relative energies; Unk, unclear or not described in available published material.

Charge Development Methods (Charges): RESP, RESP fitting; ESP, ESP fitting; M, Mulliken charge calculation; AC, AMB1 charge fitting method; GC, Gasteiger charge calculation; SIE, solvent interaction energy optimization; CS, crystal structure reproduction charge fitting; ED, experimental dipole fitting; MO-LCAO, MO-LCAO charge fitting method; MNDO, MNDO charge fitting method; CNDO/2, CNDO/2 charge fitting method; QD, quantum dipole reproduction charge fitting; QMamb, ambiguous quantum mechanical method; ENE, electronegativity equalization (similar to Gasteiger charge calculations); Unk, unclear or not described in available published material.

Hydrogen Bond Functions (H-Bond): 12-10HB, 12-10 H-bond potential; 12-6HB, adjusted repulsions using a 12-6 potential; UbsHB, Urey–Bradley–Shimanouchi H-bond potential; MpHB, Morse potential; 6-4HB, 6-4 H-bond potential.

Other Force Field Functions or Special Concerns (Other): $\alpha\beta$ different atom types for α and β . LP, lone pairs; UA, united atom; U-B, Urey–Bradley function; ETC, additional terms beyond the scope of this review.

TABLE 3
Overview of the Goals of the Studies Surveyed in the Recent Applications Section

Reference	Systems Studied	Carbohydrate Studied	Experimental Comparisons	Experimental Analysis
<i>Ambiguous Force Field</i>				
<i>Biological System</i>				
124	Synthetic receptors of β -D-mannopyranosides	β -D-mannopyranoside	Binding conformations	NOE
125	Binding to rRNA	Aminoglycoside antibiotics	Cross-sectional area	Identify mass spectrometric peaks based on observed cross sectional area
126	Cell wall teichoic acid	Teichoic acid, octameric and dodecameric (1-5)-linked poly-D-ribitolphosphate-GlcNAc chains	Binding of cationized ferritin by cells, cell packing	Relationship of D-Ala substitution to charge distribution, flexibility and extension
127	Enzymatic synthesis of carbohydrates	Dimers of glucose and galactose	Binding free energies and crystal structures	All computational study
128	Effect of sulfation on conformation relevant to sea urchin fertilization	α -L-Galp(1-3) α -L-Galp, both plain and fully 2-sulfated. Also β variants with single-site 2-sulfation	NMR solution conformers	Lack of polysaccharide cross-reactivity in the acrosome reactions of two sea urchin varieties.
129	Ribosomal complex to aminoglycoside	Paromomycin	Binding characteristics, site preference	All computational study
130	Hydrated POPC bilayer with trehalose	Trehalose	Effect of trehalose on bilayer during drying	All computational study
131	L-arabinose isomerase	L-arabinose and D-galactose	Binding site selectivity, catalytic efficiency	H-bonding used to explain binding characteristics
132	β -lactose on scaffolds complexing to lectins	β -Lactose	Influence of size, spacing and conformation on binding	Binding in assays and associated with inhibition
133	Concavalin-A structure	Unknown	Validated Concavalin-A structure from another study	Uncertain
134	β -1-3-Exoglucanase saccharide interactions	Laminarin from monosaccharide to hexasaccharide (β -GlcP-1-3- β -GlcP)	Binding mode and changes in flexibility in side-chains upon binding	All computational study
135	Galectin-1 bound to lactose	Lactose	NMR, CD, ITC, Different binding coefficient for 2nd site	
136	L-arabinose isomerase	L-arabinose	Mutant protein strain binding	Hydrogen-bonding in binding site
<i>Other Technological Study</i>				
137	Enzymatic biofuel cell anode	Glucose	H ₃ O ⁺ diffusivity versus glucose concentration	All computational study

Reference	Systems Studied	Carbohydrate Studied	Experimental Comparisons	Experimental Analysis
138	Pigment/co-pigment interactions	Malvidin-3-glucoside malvidin-3,5-glucoside	Binding constants	Comparison of structural characteristics to binding data
<i>Physical or Chemical Property</i>				
139	Inclusion complexes of (-)-menthyl-O- β -D-glucopyranoside in cyclodextrin	Cyclodextrin, menthyl glucopyranoside	Validation of computational geometry by NMR and X-ray	
140	Amylose phase change in water	Amylose	Differential scanning calorimetry	Differential scanning calorimetry
141	β -cyclodextrin interacting with amylose during a phase change	β -cyclodextrin	Differential scanning calorimetry	Differential scanning calorimetry
The CHARMM Force Fields				
<i>Biological System</i>				
142	Unfolding dynamics with and without fucosylation	L-Fucose	Stabilization of protein against thermal denaturation	All computational study
143	Glucosamine-6-phosphate synthase binding	Glucose-6-phosphate	Influence of binding on protein-wide motions	All computational study
144	Complex of BLGAL and β (1-4)-galactononoase (GAL9)	β (1-4)-galactononoase	Substrate recognition	Substrate recognition
145	Na ⁺ -coupled galactose symporter	Galactose	Protein binding conformation and Na ⁺ position	All computational study
146	Human Galectin-1 complexed with oligosaccharides	Galactose-containing ligands	Mode of interaction	All computational study
147	Oxylglucoside bound to the S2 site of LeuT	n-octyl- β -D-glucopyranoside	Conformation of extracellular-facing component of transporter	Differences in binding characteristics between substrates and inhibitors
148	Ribose permeation of membranes	Ribose, arabinose, xylose	Differences in observed bilayer permeation rates	All computational study
149	Human pulmonary surfactant protein D	Glucose	Glucose unbinding spring force	All computational study
150	Glycosylated prions	Chitobiose	Prion aggregate structure and stability	All computational study
151	Cellulohydrolase acting on cellulose strands	Cellulose	Catalytic mechanism, enzyme motion on substrate	All computational study
<i>Other Technological Study</i>				
152	Self-assembly of alginic acid wrapping a single-walled carbon nanotube	Alginic acid	Interaction characteristics and effect of alginic acid on solubility	All computational study
153	Glucose in water interacting with silica nanochannels	β -D-glucose	Glucose adsorption and diffusion	All computational study
<i>Physical or Chemical Property</i>				
154	⁴ C ₁ to ¹ C ₄ transition	α -D-glucopyranose	Compared energies to B3LYP-DFT 6-311++G**	Comparison to other computational results

Reference	Systems Studied	Carbohydrate Studied	Experimental Comparisons	Experimental Analysis
155	Solvated methyl B-cellobioside and laminarabioside	Methyl B-cellobioside, methyl B-laminarabioside	J-coupling	
156	Cellulose and lignin fibrils	Cellulose and lignin	Computational scaling	Comparison to other computational results
157	Carbohydrate polymer stretching	Pustulan	Atomic force microscopy (AFM)	
The GLYCAM Force Fields				
<i>Biological System</i>				
158	Glycoside hydrolases	β D-glucopyranose	Reaction itinerary	All computational study
159	Conformational entropies of lactose bound in Galectin-3	Lactose	Order parameters, configurational entropy change in protein	Analyzed NMR data
160	HA from HSN1 strain VN1194 (PDB 2IBX) plus mutants bound to α 2,3-sialylactose	α 2,3-sialylactose	Affect of binding site mutation on dissociation constant	All computational study
161	Tick-borne encephalitis virus	N-acetyl-D-glucosamine	GAG binding specificity	Lack of effect on GAG binding of a substitution expected to have effect
162	Galanthus nivalis agglutinin (GNA), a mannospecific lectin	Mannopentaose	Known binding, examined stability of complex	All computational study
163	Glycoprotein folding	Linear and triantennary structures of Glc, Man and GlcNAc	Conformational properties of the structures	
164	Nasturtium TmNXG1 complexes, family GH16 xyloglucan endo-transglycosylases and endo-hydrolases	Xyloglucan octasaccharide XLLG-XLLG (Fry, et al nomenclature)	Substrate recognition	
165	Human Galectin-I mutants in complex	β -Galactose, β -lactose, α -N-acetyllactosamine, α -lacto-N-biose, α -galacto-N-biose	Mode of interaction, ITC and NMR binding affinities	
166	Inverting GH8 endoglucanases	Cellopentaose	Reaction mechanism, transition state glycan conformation	All computational study
167	Xyloglucosyl transferases	Xyloglucans	Binding site selectivity	Kinetics data
168	m4-Cyanovirin-N Mutants Complexed with Di-Mannose	α -D-Manp-(1-2)- α -D-Manp	Mode of interaction	All computational study
169	Cellobiohydrolase and crystalline cellulose	Cellulose	Binding interactions	All computational study
<i>Physical or Chemical Property</i>				
170	Solvated methyl- α -L-iduronic acid, methyl- β D-glucuronic acid	Methyl- α -L-iduronic acid, methyl- β D-glucuronic acid	Conformational free energies and equilibrium conformations	All computational study
171	Glucopeptides using non-natural amino acids	β D-Glucopyranoside linked to a non-natural amino acid (with a cyclobutane side chain- ^c 4Ser ^r).	NOE, J-coupling	NOE, J-coupling
172	Carbohydrates dissolved in ionic liquids	Cellulose	Thermodynamic properties	All computational study
173	Solvated unsulfated chondroitin	Unsulfated chondroitin	NOE	NOE

Reference	Systems Studied	Carbohydrate Studied	Experimental Comparisons	Experimental Analysis
174	Solvated methyl-D-arabinofuranoside	Methyl-D-arabinofuranoside	Solution conformers derived from NMR	All computational study
175	Xyloglucan/alcohol solutions in water	(XLLG)3 (a xyloglucan)	Gel formation in alcohol solutions	All computational study
176	Cellobiose in polar environments	Cellobiose	Conformational "experimentally observed behavior of cellulose in these solvents"	All computational study
The GROMOS Force Fields				
<i>Biological System</i>				
177	Inhibition of β amyloid peptide aggregation	Trehalose	Known inhibition of trehalose to aggregation	All computational study
178	Mannose-binding plant lectins	α -D-Manp-(1-6)- α / β -D-Manp	NMR	J-coupling
179	Temperature dependence of xylan/xylanase binding	Xylobiose	Changes in protein dynamics upon binding (binding mode)	All computational study
180	UDP-galactopyranose mutase activity	UDP-Galp and UDP-Galf	Binding mode and dynamics changes on binding	STD-NMR
<i>Physical or Chemical Property</i>				
181	Cellulose, crystalline and polymer, in water	Cellulose	Atomic force microscopy pulling of cellulose polymer along/from the crystalline form	All computational study
182	Vacuum and solution conformers	Various biologically relevant	Compare to MM3 maps	All computational study
183	Hyaluronic acid with alkyl side chains	Hyaluronic acid derivatives	Gel-forming mechanism	Gel-formation at low concentrations when alkylated
The MM Force Fields				
<i>Biological System</i>				
184	Lectins and N-glycans	Bi9, BiB10, BiFi10, BiBF11 (N-glycan nona-, deca- and undeca-saccharides)	Indirect comparisons of conformational properties to external results	Influence of conformation and dynamic properties on affinity
185	Opioid receptors	6-morphinyl-R-D-mannopyranoside, morphine-6-glucuronide	Affinity to opioid receptor	NMR, conformations
186	α -O-linked Glycopeptide mimetics	Various	NMR docked structure	All computational study
187	Influence of hydrolases on structure	Maltose, methyl- α -acarviosinide, cellobiose, thiocellobiose	Known catalytic structures and known torsions	Validate suggested vaccine (carba)
188	Carba-analogue of the trisaccharide repeating unit of <i>Streptococcus pneumoniae</i> 19F CPS	(α -4)- β -D-ManpNAc-(1-4)- α -D-Glcp-(1-2)- α -L-Rhap-(1-OPO3- γ), and carba-Rhap variant	Compare motional properties between natural and carba	
189	Glycosidase inhibition	Derivatives of GlcNAc	Presence of binding conformation in solution phase ensemble	
<i>Physical or Chemical Property</i>				

Reference	Systems Studied	Carbohydrate Studied	Experimental Comparisons	Experimental Analysis
190	Crystalline state	D-sucrose, D-glucose	Thermal degradation kinetics	Differential thermal analysis, thermogravimetric analysis
191	Amorphous solid sucrose under compression	Sucrose	Crystallization	Effects of compression on crystallization
192	Cyclic and linear heptase structures	α -laminarheptaose, linear and cyclic	NMR	Observed glycosidic torsions
Modified Force Fields				
<i>Biological System</i>				
193	Enzymatic synthesis	β -L-Araf-(1,3)- β -D-Xylp	STD-NMR	STD-NMR
194	Hyaluronan lyase complexed to hyaluronan	Hyaluronan	Progression of HA degradation and associated translocation of HA	All computational study
195	Fucose binding to lectin wildtype and mutant	α -L-fucose and methyl- α -L-fucoside	Difference in binding free energies	Microcalorimetry measurements
Studies Using Multiple Force Fields				
<i>Biological System</i>				
196	Liganded 3'-aminoglycoside O-phosphotransferase type IIIa [APH(3')-IIIa]	Butirosin A, amikacin	X-ray structure	Structural basis of antibiotic resistance
197	Tumor-Associated Carbohydrate Antigen Le ^a Le ^x central fragment	Methyl α -L-fucopyranosyl-(1,4)-2-acetamido-2-deoxy- β -D-glucopyranosyl-(1,3)- β -D-galactopyranoside	Flexibility in solution	ROESY distances
198	Fluorescence tagged lactoside	Lactose	Flexibility, conformational space	NMR data
<i>Physical or Chemical Property</i>				
199	Ring puckering and rotamers	2-Sulfated iduronic acid	J coupling	All computational study
Studies Employing Force Fields Not Parameterized Specifically for Carbohydrates				
<i>Biological System</i>				
200	Enzymatic activity: endo- and exo-inulinases	Inulin	Enzyme selectivity and efficiency	Catalysis and immobilization
201	N-acetylneuraminase lyase (NAL)	N-acetylneuraminic acid (sialic acid) and KDO	Substrate specificity of NAL in E. coli	All computational study
202	ADP-dependent glucokinase	Glucose	Effect of metal on catalytic mechanism	
203	Mechanism of Pse-G, a UDP-sugar hydrolase	UDP bound to sugars with structural similarity to sialic acid	Mechanism by which UDP is cleaved	Binding mode
204	Human ketohexokinase (fructokinase)	Fructose	Structural details in mutants binding	X-ray crystallographic data
205	Gentamicin with a ribosomal decoding region	Gentamicin	Method of inhibition, mode of binding and unbinding	All computational study
206	H1N1 binding site, neuraminidase	Natural chemicals with glycoside components	Binding strength	All computational study
207	Xylose isomerase	D-xylose	Thermal effects on binding and flexibility	All computational study

Reference	Systems Studied	Carbohydrate Studied	Experimental Comparisons	Experimental Analysis
208	Large sugar-like antibiotics bound to the 50S ribosomal subunit	Erythromycin A and roxithromycin	Binding free energies, binding mechanism, observed inhibition	All computational study
209	Glucokinase complexed to glucose	Glucose	Stability of the reaction environment, binding free energies	Kinetic data
210	Acidic mammalian chitinase	NAG2 and allosamidin	Energies, structure, hydrogen bonding	All computational study
<i>Other Technological Study</i>				
211	Layered nanomaterial with alginate intercalated	Alginate	Elastic properties	All computational study
<i>Physical or Chemical Property</i>				
212	Five-membered ring conformers	Ribose variants	J coupling	All computational study
213	(9'-anthracenyl)methylene acetals of sugars	Glucopyranoside, rhamnopyranoside	Conformational energies	stability of the (9',10'-dihydro-9'-anthracenyl)methylene derivatives of sugars
214	Gluconic acid in solution	Gluconic acid (linear form only)	Raman optical activity spectrum	Raman optical activity spectrum
215	Monosaccharides in solution	36/64 mixture of α and β Glucopyranose in SPC/E waters	Diffusion, concentration-temperature analogy in bioprotection	
216	Cyclodextrins and substituted cyclotrehalans	Cyclodextrin and substituted trehalose made cyclic via the substitution	Flexibility and cavity size in cyclic glycans	
217	Solvated rebaudioside (sweetener from Stevia)	Rebaudioside	NMR	J-couplings
<i>The OPLS-AA Force Fields Biological System</i>				
218	Lectin binding	Substituted mannoside oligomers	Binding characteristics	Binding characteristics
<i>Physical or Chemical Property</i>				
219	Glucose in ionic liquids	Glucose	Viscosities at different temperatures and concentrations	
220	Fructose solution	Fructose	Solution macro-structures and dynamics vs concentration	All computational study
<i>Studies Employing Other Carbohydrate Force Fields</i>				
<i>Physical or Chemical Property</i>				
221	Solvated 2,6-hydroxyethyl cellulose	2,6-Hydroxyethyl cellulose	IR spectrum	All computational study
222	Cellulose sheets	Cellulose	Reorganization into sheets in aqueous environment	All computational study

Studies are classified according to the CarbFF family used (see Tables 1 and 2) as well as to the class of system studied. The systems studied are classed according to whether they focused on a biological application, some other technological application, or if they studied the carbohydrate from a more purely physical or chemical viewpoint. If they used their calculation to assist in the direct interpretation of experimental data, that is also noted in the Experimental Analysis column.

TABLE 4

Details of the Calculations and the Force Fields Used in the Studies Surveyed in the Recent Applications Section

References	Calculation Type	Codes	Force Field Notes	General Notes
<i>Ambiguous Force Field</i>				
<i>Biological System</i>				
124	Monte Carlo, MM, conformer search	NMR, A, Ve, Sig	Text references the 'AMBER* force field' in Maestro, ²²⁹ but the FF reference is to a general announcement of AMBER ²³⁰ .	It seems unlikely that they used an entire FF. Rather, they employed a method, Brownian dynamics, that uses only charges and radii, these having been assigned using the ANTECHAMBER ²⁴⁰ utility in AMBER 8.
125	MD	PS, A, Min	Authors report using AMBER 7 ²³¹ in Hyperchem, ^{232*} but give no further details regarding FF.	
126	Conformer search, MC torsional sampling	A, Ve, C, Min	Text references the Merck Molecular FF in MacroModel 9.11, ²³³ but the FF reference is actually for an implicit solvation method. ²³⁴	
127	MD, Docking	PS, Ve, C, All	Authors state that all simulations are performed with (a) PARM99 ²³⁵ (incorrectly referenced ²³⁶) and GLYCAM04, ⁴⁷⁻⁴⁹ and (b) with Cornell ²³⁶	
128	MD	NMR, A, Ve, C, Min	Specify GROMOS96, ²³⁷ but not GROMACS version (only the 2005 announcement ²³⁸), so FF is uncertain.	
129	Brownian Dynamics	PS, Ve, C, All	The text refers to the "Amber8 force field," ²³⁹ but not the specific FF. They used the entire FF for minimization only. After that, they used only the charges and radii assigned using the ANTECHAMBER ²⁴⁰ utility in AMBER 8.	Used high temperature molecular dynamics to build an ensemble of conformers to dock.
130	MD	Ve, C, All	Specify GROMACS 4.0, ²⁴¹ but do not specify FF.	
131	Docking +, MD	PS, C, Min	Authors reference a 1983, non-CarbfF version of CHARMM, ²⁴² but are using software published in 2008. Though they may have used the 1983 FF, this sort of mis-referencing is a common error.	
132	Conformer searches	A, C, Min	Authors report using "The AMBER force field in MacroModel", but give no reference for AMBER, the FF or MacroModel.	
133	MD	A, Min	Specify GROMACS 3.3.1, ²³⁸ but do not specify FF.	
134	MD	PS, C, All	The text says they used GLYCAM04 from GlycamWeb, but the reference is for GAFF. ²⁴³ They also reference GLYCAM-Web for a structure, but it is uncertain whether they used the GLYCAM force field in association with the structure.	Use of a carbohydrate in simulation is uncertain. Molecular images clearly represent a bound glycan ligand, but the PDB ID they reference (3CNA) does not contain a ligand, nor do they specify how the ligand coordinates were obtained.
135	MD	PS, NMR, C, Min	Used parameters from the reference ²⁴⁴ which a study of crystallographic conformations of sugars.	
				Found allosteric influence of binding at first site on binding at second site

References	Calculation Type	Codes	Force Field Notes	General Notes
136	Docking, MD	PS, A, Ve, C, Min	Authors reference a 1983, non-CarbFF version of CHARMM, ²⁴² but are using software published in 2008. Though they may have used the 1983 FF, this sort of mis-referencing is a common error.	Used simulation to guide mutation in their experimental design
<i>Other Technological Study</i>				
137	MD	C, All	The computational details in this article are sparse. The authors indicate using Hyperchem and DL-POLY, but do not provide further information or references regarding the glycan FF.	The results from the simulation appear to be unrealistic.
138	MD	A, Sig	Authors indicate using GAFF (no reference given) with recalculated RESP charges ¹²¹ in AMBER 8, ²⁴⁵ but also indicate using the Cornell FF. ²³⁶	
<i>Physical or Chemical Property</i>				
139	MD	NMR, Conf, Ve, Sig	Not referenced in article, but is most likely CVFF from 1988. ^{7,246}	The purpose of this study was to use experimental data to validate a computational method
140	MD	A, C, Sig	Article indicates using the AMBER FF in Hyperchem 8.0*.	
141	MD	A, Sig	Article indicates using the AMBER FF in Hyperchem 7.5*.	
<i>The CHARMM Force Fields</i>				
<i>Biological System</i>				
142	MD	PS, Vc, C, All	Their reference ²⁴⁷ is not the FF, but that article refers to a CHARMM CarbFF from 2001. ²⁸	
143	Normal modes	PS, Ve, C, All	The article they reference ²⁴⁸ contains neither a CarbFF nor a reference to one, but we believe that they refer to a CHARMM CarbFF from 2001. ²⁸	
144	MD	PS, A, Sig	CHARMM CarbFF from 2002. ²⁹	
145	MD	PS, C, All	CHARMM CarbFF from 2002. ²⁹	
146	MD	PS, C, All	We were unable to obtain a copy of their reference, ²⁴⁹ but since its authors are involved in CHARMM CarbFF development, we are giving the benefit of the doubt.	
147	MD	PS, A, Min	CHARMM CarbFF from 2002. ²⁹	
148	MD	Vc, C, All	CHARMM CarbFF from 1988. ²⁴	
149	Steered MD	PS, Vc, C, All	CHARMM CarbFF from 2008. ³¹	
150	MD	PS, Vc, C, All	CHARMM CarbFF from 2002. ²⁹	
151	MD	PS, Vc, C, All	CHARMM CarbFF from 2002. ²⁹	This study knowingly pushes at the limits of current computational capabilities
<i>Other Technological Study</i>				
152	MD	Vc, C, All	CHARMM CarbFF from 2002. ²⁹	
153	MD	Ve, C, All	CHARMM CarbFF from 2001. ²⁸	

References	Calculation Type	Codes	Force Field Notes	General Notes
Physical or Chemical Property				
154	New technique based on REMD	Conf, Ve, All	CHARMM CarbFF from 2008 ³¹ f	They call their technique "reaction path optimization with holonomic constraints and kinetic energy potentials"
155	MD, Adiabatic maps	NMR, Conf, Ve, C, Sig	CHARMM CarbFF from 2002. ²⁹	
156	MD	Ve, All	CHARMM CarbFF from 2002. ²⁹	This is an investigation of simulational scaling, including checks for consistency in observables
157	Replica exchange with umbrella sampling	Ve, Sig	CHARMM CarbFF from 2002. ²⁹	
The GLYCAM Force Fields				
Biological System				
158	MD, QM-MM	PS, C, All	GLYCAM93, published in 1995 ⁴⁶	Comparison of several methods for calculating conformational entropy
159	MD	PS, NMR, Ve, A, Sig	GLYCAM06, published in 2008. ⁵¹	
160	MD	PS, Ve, C, All	GLYCAM06, published in 2008. ⁵¹	Prediction of dissociation constants
161	MD	PS, A, Min	GLYCAM06, published in 2008. ⁵¹	
162	MD	PS, Ve, C, All	GLYCAM04, published in 2001 ⁴⁷	Predict details of binding in a system not easy to crystallize
163	MD	PS, NMR, Vc, C, Sig	GLYCAM93, released in 1995 ⁴⁶	
164	MD	PS, Ve, C, Sig	The article gives the precise parameter file (Glycam 04l.dat), but reference both GLYCAM04 ⁴⁷ and GLYCAM93. ⁴⁶	Predict details of binding in a system not easy to crystallize
165	MD	PS, NMR, Ve, C, Sig	GLYCAM06, published in 2008. ⁵¹ Used a CHARMM FF for the protein.	
166	MD	PS, Ve, C, All	GLYCAM06, published in 2008. ⁵¹	The purpose of this study is the validation of an FF made for ionic liquids
167	Docking, only, so not whole FF used	PS, A, Vc, C, Sig	GLYCAM06, published in 2008. ⁵¹	
168	MD	PS, Vc, C, All	GLYCAM06, published in 2008. ⁵¹	The purpose of this study is the validation of an FF made for ionic liquids
169	Docking, MD	PS, Vc, C, All	GLYCAM04, published in 2001 ⁴⁷⁻⁴⁹ (all three references are valid).	
Physical or Chemical Property				
170	New method, REMD (Hamiltonian) + ABMD	Conf, Ve, All	GLYCAM06, published in 2008. ⁵¹	The purpose of this study is the validation of an FF made for ionic liquids
171	MD-tar	NMR, A, Vc, Min	The methods section indicates use of 'Amber94' (PARM94 ²³⁶) and GAFF. ²⁴³ They also mention 'Glycam04', but reference GLYCAM93 ⁴⁶	
172	MD	Ve, C, All	GLYCAM93, released in 1995 ⁴⁶	The purpose of this study is the validation of an FF made for ionic liquids
173	MD	NMR, Conf, A, Min	GLYCAM06, published in 2008. ⁵¹	

References	Calculation Type	Codes	Force Field Notes	General Notes
174	MD	NMR, Conf, Ve, All	GLYCAM93, released in 1995 ⁴⁶	
175	MD	Vc, C, All	Used GLYCAM04, referencing i ^{48,49} and GLYCAM93. ⁴⁶	
176	MD	Conf, Ve, C, All	The authors reference the GlycamWeb parameters download site (currently at: http://glycam.org/params), but that site contains many parameter sets, and they do not specify which they downloaded.	
The GROMOS Force Fields				
<i>Biological System</i>				
177	MD	PS, Vc, C, All	Article references the 2005 GROMACS announcement ²³⁸ and GROMOS96. ²³⁷	
178	MD	PS, NMR, A, Ve, C, Sig	Article references the 2005 GROMACS announcement ²³⁸ and an encyclopedia entry for GROMOS96. ²⁵⁰	
179	MD	PS, Vc, C, All	GROMOS96, 43a1, published in 1996 ²³⁷	
180	MD	PS, NMR, A, Vc, Min	GROMOS96, 53A6, published in 2004. ⁵⁸ The authors modified it to include parameters for UDP and UDP-Galp. Since they did not modify parameters for the carbohydrate, this is classified, here, as GROMOS.	
<i>Physical or Chemical Property</i>				
181	MD (steered-type)	A, Vc, All	GROMOS96, 45A4, published in 2005 ⁵⁹ and 45A3, published in 2000. ⁵⁷	
182	MD	Conf, Ve, C, All	GROMOS96, 43a1, published in 1996 ²³⁷	
183	MD	A, Vc, Min	GROMOS96, 45A4, published in 2005. ⁵⁹	
The MM Force Fields				
<i>Biological System</i>				
184	MD	Ve, Sig	The article references a comparative study of MM3 implementations published in 2004. ²⁵¹	This is mostly a review article. The simulation is in relation to a proposed method for fingerprinting complex glycans based on glycosidic torsions.
185	MM PE maps of phi-psi	A, Min	They reference a article from 1990 ²³³ for Macromodel, and reference MM3 from 1989. ²⁵² The carbohydrate portions of MM3 were published in 1990. ⁸⁷	
186	MD, Docking	NMR, A, C, Min	They indicate using a version of Maestro from 2005, ²⁵³ and the MM3 references are to a pre-carbohydrate article ²⁵² and an NMR spectroscopy reference. ²⁵⁴	Used simulation to choose possible mimetics
187	PE maps, etc	PS, Ve, C, All	MM3 carbohydrate extensions published in 1990. ⁸⁷	
188	MD	A, Vc, C, Sig	No references were provided for FF or for the software. They indicate Hyperchem 7.5*, which was released in 2003 according to their website.	
189	MM structure search with MC-MM	NMR, Ve, C, Min	No references were provided for FF or for the software. They indicate using MacroModel 8.1.	MC-MM means Monte Carlo - Multiple Minimization
<i>Physical or Chemical Property</i>				

References	Calculation Type	Codes	Force Field Notes	General Notes
190	MM	A, Min	The indicate using second-order Møller–Plesset (MM2) and MMP2 and refer to a article from 1982. ²⁵⁵ The carbohydrate portions of MM2 were published in 1984. ⁸⁶	
191	MD	A, Ve, Min	They reference MM2 from 1977. ²⁵⁶ The carbohydrate portions of MM2 were added in 1984. ⁸⁶	Noted persistent ring deformation in their simulations
192	MD	NMR, Conf, A, Vc, Min	No references given for the FF or software. They indicate using TINKER and provide a web site address for the software.	
Modified Force Fields				
<i>Biological System</i>				
193	MD	PS, NMR, A, C, Sig	They based the FF they used on GLYCAM06, ⁵¹ but made several modifications (see article) including a charge assignment method ^{12,1} that is inconsistent with GLYCAM parameter development.	Used simulation as inspiration for enzyme-substrate recognition experiment
194	MD, "free", ED, force-probe MD, umbrella sampling	Vc, C, All	They modified OPLS ^{257,258} FFs for proteins so that they could be used with carbohydrates.	
195	MD	PS, A, Vc, C, Sig	They modified GLYCAM04 ⁴⁷ with charges calculated using a method ²³⁵ inconsistent with GLYCAM parameter development.	
Studies Using Multiple Force Fields				
<i>Biological System</i>				
196	Minimization for x-ray and MD	PS, A, C, Sig	They reference MM2 from 1977 ²⁵⁶ and 1982. ²⁵⁵ The carbohydrate portions of MM2 were added in 1984. ⁸⁶ They also used GROMACS 3.3.1, ^{259,260} specifying the 'GROMACS 87' FF without a reference.	Built a predicted bound structure for a not yet crystallized protein and ligand
197	PE surfaces (grid and stochastic), MD	NMR, A, Ve, C, Sig	PIM (TRIPOS) Carbff from 1991, ⁹¹ PARM94 (AMBER) FF from 1995 ²³⁶ and GLYCAM04 Carbff (as stated in the text though the reference is to GLYCAM93 ⁴⁶).	They also compared to MM3 potential energy maps from an external source. ²⁶¹
198	MD, NOE analysis	PS, NMR, A, Sig	CVFF and CFF91 FF's (reference is to a comparative study from 1995 ²⁶²) and MM3 (reference is to a pre-carbohydrate MM3 from 1989 ⁵²).	
<i>Physical or Chemical Property</i>				
199	MD	NMR, Conf, Ve, All	They compared GROMOS96 ²³⁷ from GROMACS 3.3 ²⁶³ to a modification of GLYCAM06. ⁵¹ From the procedure outlined in the text it is unclear whether the authors used the software to produce ensemble-averaged charges as are required for GLYCAM.	Studies Employing Force Fields Not Parameterized Specifically for Carbohydrates
<i>Biological System</i>				
200	MD, Docking	PS, A, C, Sig	PARM94 ²³⁶ (AMBER FF).	
201	MD, Docking	PS, C, All	The text refers to using CVFF in InsightII (Accelrys software), but they provide no FF references. The InsightII reference is to the user manual from 2000.	
202	MD	PS, C, Sig	Reference is to a non-carbohydrate implementation of CHARMM. ²⁶⁴	

References	Calculation Type	Codes	Force Field Notes	General Notes
203	QM/MM MD-MD on the whole system for a short initial geometry optimization	PS, A, C, Min	They reference PARM94 ²³⁶ and GAFF ²⁴³ (both AMBER FF's), saying they generated charges using the AM1-BCC ²⁶⁵ method.	Used simulation to guide mutation in their experimental design
204	Minimization	PS, A, C, Min	PARM94 ²³⁶ (AMBER FF).	
205	REMD	PS, Ve, C, All	They used AMBER 8, ²⁴⁵ and a port ²⁶⁶ of PARM99 (no reference given, but is from 2000 ²³⁵) to GROMACS.	Study suggests a stochastic gating mechanism
206	MD, Docking	PS, Ve, C, All	No references given for the FF, but the text indicates GAFF ²⁴³ and PARM99 ²³⁵ from AMBER. ²³⁰	
207	MD	PS, Vc, C, All	The text refers to CHARMM22, saying that it was published in 1992, but the reference is to a CHARMM22 FF (not referenced).	
208	MD and MM-PBSA	PS, Vc, C, All	GAFF ²⁴³ with charges generated using a variant of RESP (no reference for RESP in the text).	
209	MD (also QM/MM and MM-PBSA)	PS, A, Ve, C, Sig	They assigned charges using RESP ¹²¹ and assigned other parameters 'by analogy or through interpolation, from those already present in the AMBER force field' (ref to PARM99 ²³⁵).	
210	MD and docking	PS, C, All	The text refers to using CVFF in InsightII (Accelrys software), but they provide no FF references. The InsightII reference is to the user manual from 2000.	
<i>Other Technological Study</i>				
211	MD	Ve, C, All	CVFF from 1988. ²⁴⁶	
<i>Physical or Chemical Property</i>				
212	tar-MD	NMR, Conf, A, Ve, All	GAFF, ²⁴³ with charges using the AM1-BCC method. ²⁶⁵	
213	MD	Conf, A, Min	GAFF ²⁴³ (reference not given in text) from AMBER 10. ²⁶⁷	
214	MD, part of multi-scale spectrum simulation method	A, Ve, Sig	'Amber95' (PARM94 ²³⁶), 'Amber99' (PARM99 ²³⁵) and Amoeba ²⁶⁸ as implemented in TINKER. ²⁶⁹	
215	MD	Ve, C, Sig	CSFF from 1996 ²⁷⁰	
216	MD	NMR, Conf, C, Min	GAFF ²⁴³ from AMBER 6, ²⁷¹ supplemented with GAFF parameters from AMBER 8. ²⁴⁵ They generated ESP charges using Hartree-Fock/6-31G*.	
217	MD	NMR, Conf, A, Sig	The text specifies MMFF from 1994 as implemented in Sybyl 7.3 (Tripos software), but no reference is given	
<i>The OPLS-AA Force Fields</i>				
<i>Biological System</i>				
218	Conformer search, minimization	A, Vc, C, Min	They reference a article from 1996 ²⁷² that used FF parameters from the 1997 OPLS-AA CarbFF. ⁶⁵ yet to be released.	Found an effect of glycan rigidity on binding
<i>Physical or Chemical Property</i>				
219	MD	Ve, Sig	OPLS-AA from 1997. ⁶⁵	
220	MD	Conf, Ve, C, All	OPLS-AA from 1997. ⁶⁵	

References	Calculation Type	Codes	Force Field Notes	General Notes
Studies Employing Other Carbohydrate Force Fields				
<i>Physical or Chemical Property</i>				
221	MD, QM, normal modes	A, Ve, All	The authors generated their own carbohydrate FF parameters for use within MM + as implemented in Hyperchem 7.5*	
222	MD	Ve, C, All	No references given for either the software (Accelrys) or the FF (COMPASS, from Accelrys). No version information given, either.	

According to HyperChem technical support (BL Foley, personal communication, 2010), HyperChem employs an early AMBER FF¹⁵ for sugars.

Details of the calculations and the force fields are grouped in the same manner as in Table 3.

Abbreviations: A, the authors used the calculation in direct analysis of experimental data obtained during the study; All, the study was purely computational; C, the authors made a prediction or explanatory comment regarding externally produced data; Conf, the study focused on conformational properties; Min, computation formed a relatively small or minor part of the study; NMR, the study involved NMR or comparisons were made to NMR data; PS, computation involved a simulation of a carbohydrate interacting in some manner with a protein; Sig, computation formed a significant portion of the study; Ve, the researchers directly validated their computational method against experimental results; Vc, the researchers cited another study as method validation.