Chapter 2

Overview of Computer Modeling of Cellulose

Malin Bergenstråhle-Wohlert and John W. Brady

Abstract

Although it has a deceptively simple primary structure, the collective organization of bulk cellulose, particularly as it exists in cellulose fibers in the cell walls of living plants and other organisms, is quite diverse and complex. While some experimental techniques, such as vibrational spectroscopy and diffraction from partially crystalline samples, are able to provide insights into the organization of bulk cellulose, its intrinsic complexity has left many questions still unanswered. For this reason, additional probes of cellulose structure would be highly desirable. With the continuing advances in computer power through massive parallelization, and the steady progress in computer codes and force fields for modeling carbohydrate systems, molecular mechanics simulations have become an attractive means of studying cellulosic systems at the atomic and molecular level. The coming decade will almost certainly see remarkable advances in the understanding of cellulose using such simulations.

Key words: Cellulose, Computer modeling, Molecular dynamics

1. Introduction

Cellulose has long been one of the most studied of all biopolymer molecules, due to its singular importance. As the principal structural component of plant cell walls and also produced by algae, tunicates, and some bacteria, it is the most abundant biological molecule in the biosphere, and forms the basis for several major industries, including paper, wood products, and cotton fiber textiles. It also represents the most important feedstock for the industrial production of liquid fuels through biomass conversion, a topic of considerable current interest (1–3). However, in spite of extensive attention and its simple, regular homopolymeric sequence, the aggregate structure of cellulose is still incompletely known. This situation is somewhat analogous to that for water. Although the water molecule is quite simple in structure, its collective behavior is so rich and complex that many aspects of its behavior and

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biological functions are still not fully understood, in spite of the decades of intensive study that its crucial importance in chemistry and biology has warranted.

2. Cellulose Structure

The uncertainties about the structure of cellulose are due in part to the fact that the problem of its spatial organization is actually much more complex than might at first be expected. Native cellulose is generally produced in partially crystalline fibers, by rosettes of six cellulose synthetase molecules arranged hexagonally (or linearly in some algae). In higher plants, six such rosettes are further arranged in a hexagonal ring, so that the overall complex of synthetases produces 36 individual parallel cellulose chains, constituting the primary fibril structural element of cellulose. Each of these bundles of chains contains both regular, crystalline regions and less regular, amorphous regions. Cellulose has several ways to organize into ordered or crystalline structure. Native cellulose is found in two different allomorphs called Iα and Iβ (4, 5). If the cellulosic material is processed in some way, its crystal organization often changes. For instance, regenerated or mercerized cellulose forms cellulose II, and cellulose heated and treated with liquid ammonia forms cellulose III. Native cellulose I differs from these two latter crystal forms in its arrangement of the hydrogen bonding network and, as a consequence, in the conformation of the primary alcohol groups. In cellulose I, the primary alcohol group has been found to be, in principle, all TG (6) (*trans* with respect to O5 and *gauche* with respect to C4) (7, 8), and the crystal structure is a layered structure with no hydrogen bonds in between the layers (Fig. 1). Cellulose II and III are both three-dimensional hydrogen bonding networks with alternating conformations of the primary alcohol group.

In living cell walls, the cellulose fibrils have a high tendency to associate into larger fibril aggregates. The fibril aggregates intimately associate with other plant constituents such as hemicelluloses (a family of polysaccharides), lignin (aromatic polymers), and water to form the macroscopic plant fibers (9). Thus, the structure of cellulose is highly dependent on its source of origin, its processing history, and environmental conditions.

As a consequence, investigating the structure of cellulose is a difficult task, as compared for instance to the crystal structures of proteins, which are routinely determined from single crystals. First of all, as mentioned, even individual native cellulose fibrils are structurally heterogeneous, with at least two different crystal forms (Iα and Iβ) (7, 8, 10) alternating in an unknown spatial distribution with amorphous regions whose character and spatial distribution are also unknown. Second, its source of origin is

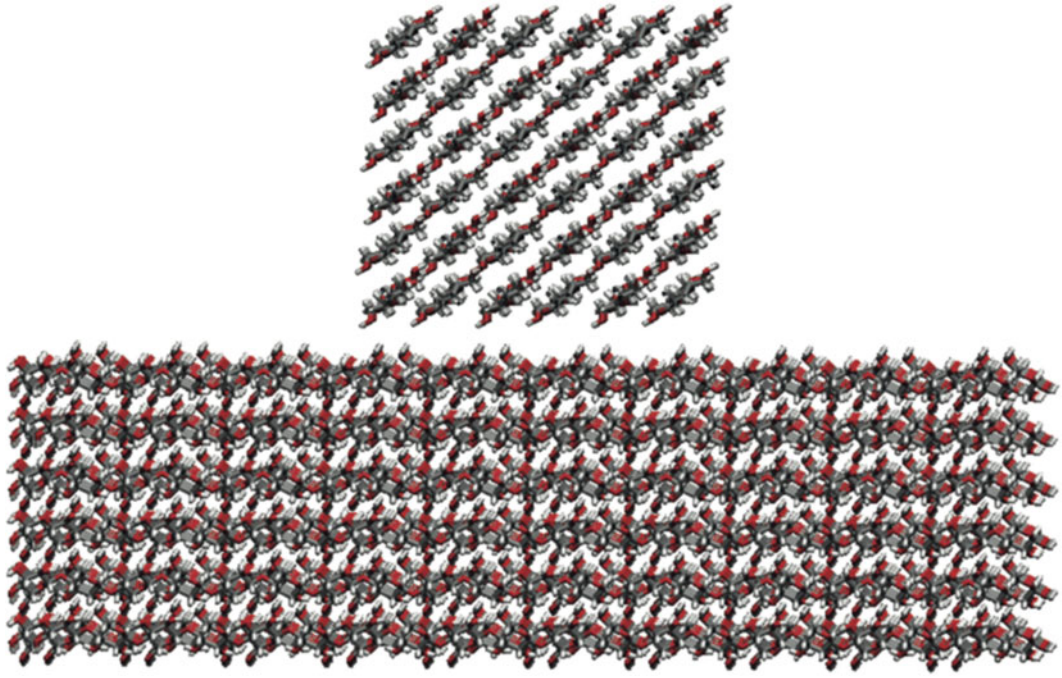

Fig. 1. Front and side view of a 36 chain cellulose Iβ crystal with DP 20.

important to the structure, since fibrils from different sources may have different sizes, different fractions of Iα and Iβ allomorphs and different crystallinity. The sample may also be more or less pure, and the processing history might have affected the original structure. In addition to this, the complete insolubility of cellulose fibrils in water under normal conditions is adds extra complexity to the task (11). As a result, the reported crystal structures for cellulose are actually fiber diffraction studies, with the determination of the molecular coordinates dependent in part on modeling and other assumptions, and are deduced from a surprisingly small number of diffraction spots in the experimental data.

While the most recent reported crystal structures (8, 10) seem plausible, some uncertainty remains. The diversity of cellulose structure is for instance highlighted by the discussions around the possible existence of a fibril twist. Experimental evidence suggests that cellulose fibrils may be twisted (12), possibly violating the assumption of a small crystal unit cell, with cellobiose as the repeat unit. The twist is mainly seen for bacterial cellulose (13) and it is not clear if the origin is biological or physical. On the other hand, there are also examples of observations where the fibrils of *Valonia* algae for instance show no twist at all (14). In addition, it has been suggested that the drying of experimental samples, necessary in the preparation of the crystalline fibrils for diffraction experiments, might result in a change in structure, producing an artifactual lattice different from that of never-dried cellulose. There is also a

general tendency to be seduced by the appearance of precision in crystal structures that might distract from a more critical evaluation of general assumptions. For example, a crystal structure for the regenerated crystal form cellulose II has been reported (10, 15, 16), based on the assumption that in this form of cellulose the chains are antiparallel. However, a study in which the reducing ends of cellulose II chains are labeled has found that the overwhelming majority of the microfibers are labeled at only one end (17), indicating parallel packing of the chains. Another recent labeling study found that as much as 15% of the chains are apparently antiparallel (labeled at both ends), but also found that the larger portion are either unlabeled, or are labeled at only one end, indicating either parallel packing or incomplete conversion (18). Resolution of such an issue is a necessary precondition for a "crystallographic" structure determination based on a minimal set of diffraction spots.

Given the many difficulties involved in the experimental characterization of cellulose structure, particularly under noncrystalline conditions, it is reasonable to turn to computational models for cellulose fibrils and crystals, in the hope that such models might further illuminate the experimental data and possibly even be able to resolve some of the uncertainties.

3. Molecular Computer Models and Simulations

Molecular mechanics computer studies now have a very long history of successful application to all manner of biological systems, including solids, liquids and liquid solutions, proteins, phospholipid bilayers, and carbohydrates, including polysaccharides like cellulose (19–30). Molecular mechanics (MM) studies, such as molecular dynamics (MD) simulations or Monte Carlo calculations, directly model the properties of molecular systems using an assumed knowledge of the way in which the energy of the system varies with the atomic coordinates. These simulations have been very useful in studying both biological molecules and liquid solutions. For example, MD simulations have been used to successfully model the folding of a small protein, the villin headpiece subdomain, in aqueous solution, which folded to approximately the experimentally known conformation over a simulation time of 1 μs (at the time requiring four CPU months on the fastest supercomputer available) (31), demonstrating that the principal limitations in the application of such methods to many biological questions are system size and simulation time scale. Modeling of this type has become an essential and integral part of pharmaceutical design and is routinely used in many technological applications.

One possible approach to the modeling of cellulose crystal structures might be to use straightforward energy minimization calculations (32). This approach adjusts the atomic coordinates of a system in the directions which reduce the forces acting on each atom until the sum of all these forces is zero, representing a local minimum-energy state. However, the potential energy hypersurfaces for cellulose crystalline packing contain an enormous number of local energy minima, many of similar energies, all separated from one another by energy barriers of varying heights. Unfortunately, there are no general procedures for finding the lowest of these local energy minima. The conformation predicted by energy minimization calculations will be a strong function of the conformation chosen as the starting point for the calculation (such as the reported crystal structures). This so-called multiple-minimum problem (33) makes successful structural predictions by energy minimization alone very unlikely to succeed.

Perhaps the most common and successful type of computer modeling of biomolecules is molecular dynamics calculations. MD simulations use the forces calculated from MM potential energy functions to numerically integrate Newton's equations of motion for all of the atoms in a system as they move in response to the forces acting on them, in order to provide a description of the evolution of a system with time. These forces are computed directly from the derivatives of an empirical potential energy function of the atomic coordinates. In such calculations, physical observables (properties) are calculated as time averages over the various states that arise during the course of the simulation, since in principle the frequency of occurrence of each state and the time spent in each state will, for simulations of sufficient length, converge to the value determined by the Boltzmann distribution. Unlike Monte Carlo calculations, MD trajectories allow a picture of how a system might evolve with time if it is not at equilibrium, and at least in principle allow the possibility of calculating rates. Also, unlike the situation with minimization studies, the momentum carried by the system in MD trajectories can allow it to cross energy barriers, allowing it to escape from local energy wells and more completely explore its full configuration space. Since entropy arises naturally from the application of Newtonian dynamics, this approach has the added advantage of sampling the free energy surface, since it is the free energy, including the entropy, which determines experimental properties. The ease with which water and cosolutes can be incorporated into MD simulations is another advantage that these calculations have over energy minimization approaches. Solvent not only serves as a heat bath, further promoting transitions over barriers, but may also be an essential component of the free energy of chain association in crystals (34).

The atomic and molecular detail available in such simulations allows unprecedented insight into the physical properties unavailable from any type of experiment. Molecular mechanics simulations

also offer other advantages over experiments. For example, in computer simulations, systems and properties can be modeled which are currently inaccessible to experiment. Furthermore, questions can be asked which could never be answered experimentally (for example, how do results depend on mass, charge, atomic radius, etc., which can be changed in a computer model but of course cannot be adjusted in reality). In some cases (however, probably not most) the simulations may be easier than the experiments and can thus increase the efficiency, for example, of selecting protein mutants to be produced by recombinant techniques, or ligands to be screened as possible drug candidates (or pretreatments, for example, in the case of cellulose modeling). Using molecular graphics, the results of such simulations can be displayed pictorially for a dramatically improved understanding of the system, which facilitates the development of conceptual models, although they should be looked upon with caution and not taken as a verity just because of their attractive appearance. It should also be remembered, however, that molecular mechanics calculations are only useful in understanding physical systems to the extent that the force fields and other approximations employed realistically model the way in which the system energy changes with atomic coordinates. It is essential to validate the results of simulations through comparison with experiment whenever possible, to increase the confidence with which those computational results which cannot be verified experimentally can be accepted.

The fundamental requirement of molecular mechanics studies of any type is a complete description of the variation of the total potential energy of the system as a function of the atomic coordinates. For macromolecules and condensed phases the accurate calculation of this quantum mechanical energy is not possible, and it is thus common to employ analytic, empirical energy functions which have theoretically reasonable functional forms and which have been parameterized to the results of experiment and simple calculations. These semiempirical potential energy functions may vary somewhat in their details; most, however, represent the intramolecular potential energy as a sum of electrostatic and van der Waals interactions between nonbonded atoms and terms for hindered rotation about molecular bonds, with bond stretching and bond bending forces derived from quadratic restoring potentials,

$$V(\mathbf{q}) = \sum k_b (b - b_0)^2 + \sum k_\theta (\theta - \theta_0)^2 + \sum k_\phi [1 + \cos(n\phi - \delta)] + \sum A_{ij} / r_{ij}^{12} - B_{ij} / r_{ij}^{6} + q_i q_j / r_{ij}. \quad (1)$$

The parameters in these potential energy surfaces, such as atomic partial charges, bond lengths and angles, and force constants, are usually obtained from quantum mechanical calculations for small molecular models that contain functional groups in analogous covalent environments. The results are then validated by extensive

comparison with available experimental data, such as crystal structures, vibrational spectra, or solvation free energies.

Several MM software packages have been developed and widely employed in modeling biomolecules, including CHARMM (35, 36), AMBER (37), GROMOS/GROMACS (38, 39), NAMD (40, 41), and TINKER (42). It should be noted that for straightforward calculations like MD simulations, the results should not depend significantly on the actual program employed, barring the accidental introduction of a programming "bug," which is remotely possible since all of these programs undergo periodic updating and development. However, the results of MD simulations might depend strongly on the energy function (force field) used to model the system, including the water model used. Enormous effort has gone into the development of ever more realistic MM energy parameters over the past few decades. Several force fields have been developed specifically to model carbohydrates and the specific covalent situations encountered in such molecules. The most widely used current carbohydrate force fields are the newly developed "Team Sugar" CHARMM parameters (43), the most recent version of the GLYCAM (44) (AMBER) parameters, and the recent GROMOS carbohydrate parameters (45). It should be reemphasized that while these sets were developed in association with specific software packages, they can in principle be used in any of the MM programs with the same results (with greater of lesser degrees of difficulty in implementation) (46).

3.1. Molecular Simulations of Cellulose

As mentioned, the most crucial limitations of MD simulations are system size and the timescale of the simulations. The equations of motion are integrated by discretizing them into a series of finite steps during which the forces can be treated as approximately constant. The forces must be calculated at each of these discrete steps, which is an expensive operation for a polymer like cellulose since the number of contributing interactions grows approximately as N^2, where N is the number of atoms. Because of the strengths of the chemical bonds involved, bond vibrations are rapid, and the size of the individual time steps between these force calculations must be quite small, on the order of 1 fs (i.e., 10^{-15} s), to ensure that the changes across the step are small. Thus, a very large number of these CPU-intensive force calculations are necessary to amount to even relatively short simulation times (hundreds of picoseconds, for example). Using current conventional computers, typical MD simulations of solvated proteins model times in the nanosecond range, although the microsecond range is within reach when using well-parallelized simulation routines on hundreds of CPUs (47). Modeling cellulose fibrils is much harder than simulating the typical protein; however, since a typical fibril chain in wood cellulose has a degree of polymerization of around 15,000. Even with only 36 such chains, and the explicit water molecules necessary

to solvate such a large aggregate, the number of atoms N is vastly larger than for even large proteins, further limiting the timescales that can be simulated. Unfortunately, however, cellulose crystals change their structures on timescales ranging from milliseconds to far longer. Thus, there is a difference of at least four orders of magnitude between the timescale of a typical MD simulation and the timescale for cellulose structural changes.

Keeping in mind these limitations, the types of questions about cellulose that might be addressed using modeling could include: what is the native fibril structure, including both the ordered or crystalline portion, as well as the amorphous fraction; what is the nature of the interactions with the hemicelluloses and lignins and the role of water in the native state; what are the effects of temperature, solvent, and cosolutes (as in pretreatments); how do cellulose fibrils interact with each other in nanostructured cellulose-based materials and how do cellulose substrate fibrils interact with cellulases? With the widespread availability of highly parallel MM software packages and the speed of parallel arrays of CPUs, all of these types of questions are becoming tractable, at least in principle, and several such preliminary studies have already been attempted. The first MM simulations of cellulose date back to only a few years after such calculations were applied to proteins (48–51), but it is only quite recently that realistic simulations of large unrestrained crystals in an aqueous environment have been possible (24, 26–30). Earlier simulations necessarily were confined to relatively small model crystals, for short times, and employing severe approximations that significantly limited any changes that might have taken place (19, 20, 52, 53). Simulations have also begun to be applied to the problem of cellulose interacting with cellulase enzymes (54–56). An overview of the *in silico* modeling of cellulose during the last decade is found within a recent review of the subject (57).

Unfortunately, at the time of this writing, it is still too early for the MM simulations of cellulose crystals that have been reported to date to definitively settle any of the remaining questions concerning cellulose structure (57). However, several general statements can be made. Perhaps the most important is that the reported cellulose Iβ crystal structure (10), when simulated for sufficient time periods, and without artificial constraints, is not stable with any of the MM force fields currently available (43–45). Apparently the heights of the barriers that separate the reported crystal structure from lower energy structures vary among the different force fields, so that the time for significant structural reorganization varies among the different models, but with enough time, all will undergo changes from the proposed crystal structure (30). Of course, it is possible that all of these force fields are wrong in some critical way, but it is worth noting that all three of the most commonly used carbohydrate force fields were developed independently, and that similar force fields for other systems, including

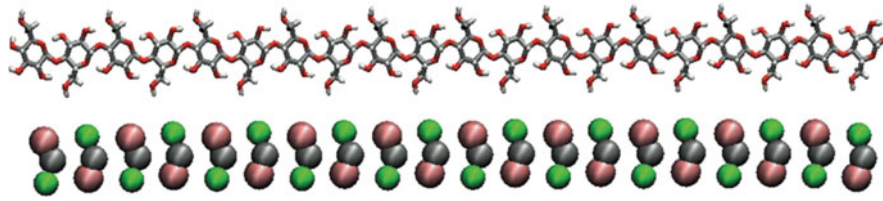

Fig. 2. A DP 20 cellulose chain represented as an all-atom model and a coarse-grained model with three interacting sites per glucose unit.

carbohydrates, have successfully reproduced known experimental properties. In addition, some of the differences observed in the MM simulations with different force fields are common across the various force fields, such as the observation of chain tilts within layers (24, 25, 30, 52), the occurrences of non-TG primary alcohol conformations (30), and the development of hydrogen bonds between layers (24, 30). Chain and fibril twists are a common feature of the MM simulations (24, 25, 30), but apparently such twisting is frozen out at longer simulation times, regardless of the force field used, as a three-dimensional, interlayer hydrogen bond network develops as the result of the reorganization of the crystal structure. Such troubling observations suggest that more work is probably needed, both in the crystallographic analysis and in the MD simulations.

Other possibilities for the profitable application of MM simulations to cellulose systems in the future would include studies of the interactions of cellulose with lignin (58) and hemicellulose, and of cellulase enzymes interacting with different types of cellulosic substrates (55). Since one of the most important limitations on MM simulations of cellulosic systems is that of size and timescale, there is the potential for extending the scope of such simulations through the use of so-called coarse grain calculations, in which certain presumably unimportant details are represented only approximately rather than in specific detail. In MM calculations, this often involves models in which molecules such as cellulose are not treated in atomic detail. Rather, groups of atoms which are presumed to exhibit a similar character and which move approximately as a unit are represented usually as a single entity, and new force fields are parameterized so as to give approximately the same results in test simulations as MD simulations at the full atomic-level detail. Figure 2 illustrates an example of such a coarse-grained representation of a cellulose chain, compared to an all-atom model. Often implicit solvation models are employed that allow the very expensive treatment of many thousands of water molecules to be avoided (59–62).

The principal advantage of coarse grain calculations is that they allow the simulation times to be substantially extended, often by orders of magnitude, which is of critical importance since, as

already observed, the most important limitation of the utility of MM simulations is the timescale that can be modeled. Already coarse grain models have been developed for cellulose (63) and used successfully to understand the interaction of a cellulose binding domain from the cellulase CBH I of *Trichoderma reesei* with a crystalline cellulose surface (64). Such methods are not yet feasible for studying intrafibrillar structure, but hold great promise for understanding such large-scale structures as cell wall fibers or cellulose fibril network materials like cellulose nanopaper or foams (65) in the future.

In addition to coarse grain simulations, a new generation of polarizable force fields is under development for all-atom simulations which account for the changing electronic structure of molecules as their local environment changes (A.D. MacKerell, personal communication). Since the changes in aggregation that occur in crystalline cellulose in MM simulations largely involve interchain and interlayer hydrogen bonding, such polarization effects may prove to be important in an ultimate understanding of the structures of cellulose. The steady increase in computer size and speed through parallelization will make long simulations of large systems progressively more practical, even with the greater computational expense of including electronic polarization.

In conclusion, advances in computer power, software design, and force field development have set the stage for molecular mechanics simulations of cellulosic systems at an unprecedented level of realism. Future calculations will potentially involve large scale models of the full complexity of cell walls, including cellulose fibers interacting with lignin, hemicelluloses, water, as well as potentially pectins and phospholipids at the interfaces. Simulations of extended realistic cellulose microfibrils, in tandem with diffraction, NMR, and spectroscopic experiments, may ultimately resolve any lingering uncertainties about the crystalline structure of cellulose, and provide insight into the nature of amorphous cellulose as well. Finally, models of the interactions of cellulase proteins with cellulose may help in the development of more efficient process for cellulose degradation in biomass conversion. The coming decade should be an exciting time indeed in the study of cellulose using MM techniques.

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