Predictive Multiscale Modeling of Nanocellulose Based Materials and Systems

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Abstract. Cellulose Nanocrystals (CNC) is a renewable biodegradable biopolymer with outstanding mechanical properties made from highly abundant natural source, and therefore is very attractive as reinforcing additive to replace petroleum-based plastics in biocomposite materials, foams, and gels. Large-scale applications of CNC are currently limited due to its low solubility in non-polar organic solvents used in existing polymerization technologies. The solvation properties of CNC can be improved by chemical modification of its surface. Development of effective surface modifications has been rather slow because extensive chemical modifications destabilize the hydrogen bonding network of cellulose and deteriorate the mechanical properties of CNC. We employ predictive multiscale theory, modeling, and simulation to gain a fundamental insight into the effect of CNC surface modifications on hydrogen bonding, CNC crystallinity, solvation thermodynamics, and CNC compatibilization with the existing polymerization technologies, so as to rationally design green nanomaterials with improved solubility in non-polar solvents, controlled liquid crystal ordering and optimized extrusion properties. An essential part of this multiscale modeling approach is the statistical-mechanical 3D-RISM-KH molecular theory of solvation, coupled with quantum mechanics, molecular mechanics, and multistep molecular dynamics simulation. The 3D-RISM-KH theory provides predictive modeling of both polar and non-polar solvents, solvent mixtures, and electrolyte solutions in a wide range of concentrations and thermodynamic states. It properly accounts for effective interactions in solution such as steric effects, hydrophobicity and hydrophilicity, hydrogen bonding, salt bridges, buffer, co-solvent, and successfully predicts solvation effects and processes in bulk liquids, solvation layers at solid surface, and in pockets and other inner spaces of macromolecules and supramolecular assemblies. This methodology enables rational design of CNC-based bionanocomposite materials and systems. Furthermore, the 3D-RISM-KH based multiscale modeling addresses the effect of hemicellulose and lignin composition on nanoscale forces that control cell wall strength towards overcoming plant biomass recalcitrance. It reveals molecular forces maintaining the cell wall structure and provides directions for genetic modulation of plants and pretreatment design to render biomass more amenable to processing. We envision integrated biomass valorization based on extracting and decomposing the non-cellulosic components to low molecular weight chemicals and utilizing the cellulose microfibrils to make CNC. This is an important alternative to approaches of full conversion of lignocellulose to biofuels that face challenges arising from the deleterious impact of cellulose crystallinity on enzymatic processing.
1. Applications of modified cellulose nanocrystals

Cellulose nanocrystals (CNC), the smallest building blocks of cellulose holding its physical properties, is a biocompatible and biodegradable material with mechanical properties comparable to those of reinforcement materials, such as carbon fibers, carbon nanotubes, and steel [1],[2]. The CNC can be produced in a sustainable and viable bulk process, unlike other nanomaterials (e.g., carbon nanotubes) that are typically produced in small amounts and at a very high cost [3]. The outstanding mechanical properties of CNC make it very attractive as reinforcing additive in nanocomposite materials [4]-[8], hydrogels [9]-[13] and foams [14],[15], as well as specialized security inks [16],[17]. Suspensions of CNC undergo phase separation into clear isotropic and structured chiral nematic phases above critical concentration [18] and upon drying from iridescent chiral nematic films [19]-[21].

Large-scale applications of CNC in nanocomposites require modifications to tune up its surface properties thus enhancing its solubility in nonpolar solvents and compatibility with polymer matrices [22]. The CNC have been extensively manipulated to provide a rich suite of new materials and platforms for further transformations [23]. Several methods for CNC surface modification have been developed, including grafting [24]-[26], self-assembly [27], and surfactants [28]. Effective surface modifications must provide sufficient solubility tune up without altering the CNC inter- and intramolecular hydrogen bonding network and deteriorating crystallinity and mechanical properties.

Despite the extensive experimental research effort, progress towards the development of effective surface modifications has been rather slow, mainly because (i) extensive chemical modifications destabilize the hydrogen bonding network of cellulose, causing deterioration of the mechanical properties, and (ii) relationship between surface modifications and solvation thermodynamics has not been explored. The 3D-RISM-KH molecular theory of solvation [32]-[36] provides an insight into CNC-water hydrogen bonding interactions relevant to relaxation and right-hand twist, and predicts the effective forces that control the dispersion of pristine and modified CNC in various solvents [29],[30].

2. 3D-RISM-KH integral equation theory of molecular liquids and solutions

Based on first principles of statistical mechanics [31], the 3D-RISM-KH molecular theory of solvation (three-dimensional reference interaction site model with the Kovalenko-Hirata closure approximation) [32]-[36] bridges the gap between molecular structure and effective forces on multiple length scales. It provides a firm platform to handle complex nanochemical and biomolecular systems in solution. As distinct from molecular simulations exploring the phase space by direct sampling, 3D-RISM-KH operates with spatial distributions in the statistical-mechanical ensemble rather than with individual trajectories of molecules. Analytical summation of the free energy diagrams beginning with molecular force field leads to the 3D-RISM-KH integral equations for 3D site correlation functions. Converging the latter gives the solvation structure in terms of 3D distribution maps of solvent interaction sites around a solute macromolecule (supramolecule) of arbitrary shape and then analytically the solvation thermodynamics in a simple closed form as a single integral of the 3D correlation functions obtained.

For simple and complex solvents and solutions of a given composition, including buffers, salts, polymers, ligands and other cofactors at a finite concentration, the 3D-RISM-KH molecular theory of solvation properly accounts for chemical functionalities by representing in a single formalism both electrostatic and non-polar features of solvation, such as hydrogen bonding, structural solvent molecules, salt bridges, solvophobicity, and other electrochemical, associative and steric effects. For real systems, solving the 3D-RISM-KH integral equations is far less computationally expensive than running molecular simulations which must be long enough to sample exchange and binding events. This enables handling complex systems and processes occurring on large space and long time scales, frequently not feasible for molecular simulations. The 3D-RISM-KH theory successfully describes both simple and complex associating liquids with different chemical functionalities [36]-[43], including ionic liquids [39] and polyelectrolyte gels [40], in a range of thermodynamic conditions and composition [41]-[43], and in various local environments such as interfaces with metal [32],[33] and metal oxide [44], zeolite [35],[45] and clay [46], and confinement of carbon nanotubes [38], synthetic organic rosette nanotubes [36],[47]-[49], and biomolecular systems [36],[50]-[62].
3. Structure and effective interactions of pristine and modified CNC in solution

A model for the computer simulation of CNC is based on the $I_\alpha$ crystal structure [63] containing 34 chains forming a three-layered cellulose fibril, as shown in Figure 1. The fibril cross section is approximately 4.3 nm in its longest direction and each chain in the fibril consists of 16 glucose units making 8 nm long particles.

![Figure 1. Cellulose fibril containing 34 glucan chains: (Left) cross section showing inner (red), intermediate (green) and outer (blue) layers; (Right) CNC particle dimensions.](image)

For this model particle, structure relaxation is performed using MD simulation in a periodic box with dimensions 14.9 nm $\times$ 8.9 nm $\times$ 8.3 nm [30]. The distance between particle surface and the box edges is 2 nm and the space in the box around the particle is filled with water molecules. The aim of this simulation is to relax and equilibrate the model structure in the presence of solvent, mimicking as close as possible the experimental conditions of pristine CNC solvation in aqueous solution. In this neutral particle, the initial charge distribution in the cellulose fibril is inhomogeneous over different faces of the particle Figure 2(a) and (b). Cellulose layers in the crystal are stacked so that the positively charged groups face the negatively charged ones, giving a “crystal-like” charge distribution. The 3D density distributions of solvent species around an unrelaxed CNC particle clearly shows that anions (Cl$^-$) are concentrated around the particle surface with exposed positively charged groups, while positively charged ions (Na$^+$) are localized on the opposite side of the particle Figure 2(c).

On relaxing the CNC particle in explicit water solution for 6 ns and analyzing the structure after relaxation, we observe a smearing of the charge over the faces, Figure 2(d) and (e), which noticeably affects the distribution of the ions around the fibril Figure 2(f). The relaxed particle charge is weakly polarized, as evidenced by the rather even distribution of cations and anions around it. In both unrelaxed and relaxed particles, the ions distributions are calculated using the 3D-RISM-KH theory for a particle in aqueous solution of NaCl at concentration 0.040 mol/kg. One can hypothesize that the initial “crystal-like” highly polarized charge distribution in the CNC particle is one of the driving forces leading to the fibril twisting.

![Figure 2. Relaxation of a pristine CNC particle in explicit water MD simulation; positively (in blue) and negatively (in red) charged atoms. Surface charge distribution of the unrelaxed CNC particle: (a) Faces exposing positively charged groups are predominantly blue colored; (b) Faces exposing negatively charged groups are predominantly red colored; (c) 3D distributions of Na$^+$ (blue) and Cl$^-$ (green) around an unrelaxed fibril in NaCl aqueous solution. Surface charge distribution of a relaxed CNC particle after 5 ns MD simulation: (d) CNC particle cross section with right-hand twist; (e) Charge distribution in the relaxed particle; (f) 3D distributions for Na$^+$ (blue) and Cl$^-$ (green) around a relaxed fibril in NaCl aqueous solution.](image)
The next step taken towards the development of representative CNC models is to build a charged sulfonated particle model, which is accomplished by grafting sulfate groups to some of the cellulose’s surface chains at the surface density taken from elemental analysis [64]. The model contains 16 modified glucose units at the C6 position with sulfate groups so as to have 4 substitutions on each face. Each sulfonate group bears one unit of negative charge and the total CNC particle charge is -$16e$. The estimated surface charge density is $0.3 \ e/\text{nm}^2$, in accordance with the experimental data for sulfonated CNC [65]. The MD setup for particle relaxation is similar to that of the neutral particle, the only difference being 16 Na$^+$ ions added to the simulation box to get overall electrostatic neutrality.

The 3D-RISM-KH theory has been applied to CNC surface modifications to tune-up the effective forces acting on CNC particles in solution. The I$\beta$ pristine and esterified cellulose was considered in hydrophilic solvent (water), hydrophobic solvent (benzene), and ionic liquid ([mmim][Cl]). Ionic liquids (IL) are a novel class of non-volatile environmentally-friendly solvents that attracted interest of synthetic chemists due to the fundamentally different reaction thermodynamics and kinetics compared to typical molecular solvents [66]. The 3D-RISM-KH method predicts the properties of IL in a remarkable agreement with the results of Car-Parrinello high-level ab initio modeling [36],[39].

![Figure 3](image3.png)  
**Figure 3.** Periodically-extended model of pristine and esterified I$\beta$ CNC.

![Figure 4](image4.png)  
**Figure 4.** Solvation structure of [mmim][Cl] ionic liquid around pristine I$\beta$ CNC particle.

![Figure 5](image5.png)  
**Figure 5.** Potential of mean force between the pristine (upper panel) and esterified (lower panel) periodically-extended I$\beta$ CNC rods immersed in water, benzene, and [mmim][Cl] ionic liquid (IL).
Figure 3 exhibits the periodically-extended Iβ CNC rod model that is particularly suitable for prediction of interaction among particles with uniform surface and large aspect ratio, using the pristine structure from Ref. [67]. The esterified structure (right-hand inset) containing acetate groups at every primary surface hydroxyl group (O6 atom, left-hand inset) is partially relaxed using molecular mechanics with constrained cellulose backbone. For every dispersion configuration, the 3D-RISM-KH theory predicts the solvent orientation based on the 3D solvent site density distributions, as shown in Figure 4 for the solvation structure of pristine CNC in methyl-methyl-imidazolium chloride IL.

Figure 5 presents the effective interaction (potential of mean force) plots for pristine and esterified CNC in different solvents. Similar to Iα cellulose, the Iβ cellulose is stabilized by the hydration shell. The pristine CNC disaggregation barrier increases in the order of solvents: water < benzene < IL, which indicates that dispersion is favorable in water but is not favorable in benzene and IL. This is typical for hydrophilic surfaces. For esterified CNC, the potential of mean force in benzene and IL have a lower disaggregation barrier than in water, leading to facilitated dispersion in hydrophobic solvents. The lack of significant solvent expulsion barriers in benzene and IL suggest weak solvent-solute interactions. This example demonstrates how surface modifications can be employed to tune dispersion properties of CNC in various solvents. In addition to addressing the type of the surface modification, the 3D-RISM-KH methodology allows prediction of the degree of surface modification necessary to achieve a certain dispersion effect. This is particularly important in industrial processing, where achieving high degrees of surface modification could be costly.

4. Effect of hemicellulose composition on nanoscale forces that control cell wall strength

Overcoming biomass recalcitrance constitutes the most fundamental unsolved problem of plant-based green technologies [68],[69]. Efficient conversion of lignocellulosic biomass to second-generation biofuels and valuable chemicals requires decomposition of resilient plant cell wall structure. Plants naturally evolved to withstand harsh external mechanical, thermal, chemical, and biological factors, and so are resistant to cell wall deconstruction. Plant secondary cell walls are composed of cellulose microfibrils embedded in a complex non-cellulosic matrix of mainly hemicellulose and lignin. These non-cellulosic components are responsible for the cohesive forces within the cell wall that entail structural support to plants [70]. It is well known that cell wall recalcitrance varies among plant species and even with different phenotypes of the same plant, depending on the chemical composition of the non-cellulosic matrix. Changing the amount and composition of branches attached to the hemicellulose backbone can significantly alter cell wall strength and microstructure [68],[70]-[72]. Therefore, full understanding of the chemical interactions within the cell walls is fundamental to gain control of the lignocellulosic biomass recalcitrance [69].

Glucuronoarabinoxylan – hemicellulose type most abundant in important lignocellulosic grasses used for biofuel production, such as sugar cane and corn – consists of a xylan backbone decorated with branches of mainly glucuronic acid and arabinose whose amount and ratio varies substantially with the plant genotype [73]. Genetic manipulation of glucuronic acid branching was shown to significantly improve xylan extractability from cell walls without impairing plant growth [70]. High-resolution imaging indicates a strong correlation between cell wall architecture and enzymatic digestibility [71].

Molecular dynamics simulations have been used to investigate decrystallization of cellulose [74],[75], the interactions between cellulose and non-cellulosic components of plant cell walls [76], and the structure and dynamics of lignin [77]. However, extremely long and costly simulations are required to get adequate statistical sampling addressing both solvation structure and thermodynamics of effective interactions in cell walls based on molecular forces. The 3D-RISM-KH molecular theory of solvation provides full statistical-mechanical sampling and molecular picture of hemicellulose arrangement around cellulose, and is uniquely capable of predicting the chemistry-driven effective interactions in plant cell walls as well as enzymatic and catalytic chemical deconstruction of biomass. It reveals molecular forces maintaining the cell wall structure and shows that hemicellulose branches of arabinose, glucuronic acid, and especially glucuronate strengthen the primary cell wall by strongly coordinating to hydrogen bond donor sites on the cellulose surface [78],[79].
Significant advances have been achieved lately for comprehension of the cell wall inner architecture and its correlation with the enzymatic digestibility. Nonetheless, due to the high complexity of the cell wall, there is still a lack of molecular level characterization of these structures. We construct a model of a primary cell wall fragment containing two 4-chain 8-glucose-long cellulose fragments immersed in aqueous solutions of the monomers arabinose, glucuronic acid and glucuronate at different concentrations [78]. Application of the 3D-RISM-KH molecular theory of solvation to this model to investigate the effects of hemicellulose composition on the effective interactions with cellulose fibrils shows the substantial role of hemicellulose in the stability of the primary cell wall. This reveals the relative contributions of different xylan substitutions to cell wall strength [78], and opens up an approach to the molecular basis of plant cell wall recalcitrance in an unprecedented level of details by considering more elaborate cell wall models and including lignin into account [79]. The effective interactions and the aggregation free energy of cellulose nanofibrils in hemicellulose hydrogel (Figure 6) show that the main effect of hemicellulose composition arises due to the presence of basic groups but not stereochemistry [78]. Extension to other classes of hemicelluloses such as galactoglucomannans suggests the effect of galactose, glucose and mannose would be rather weak and the largest contributions would arise from the carboxylate groups of random glucuronate substitutions.

Recent approaches to overcome biomass recalcitrance involve genetic modification of crops to control lignin contents or composition and xylan structure so as to enable less severe pretreatment and efficient enzymatic processing [70],[80]. Lignin extraction from transgenic plants at mild conditions is expected to enable enzyme access to the hydrophobic cellulose face while keeping the remaining cell wall structure intact and the polysaccharides least altered for effective digestion by enzymes [71]. We envision integrated biomass valorization based on extracting and decomposing noncellulosic components to low molecular weight chemicals and using cellulose microfibrils to make cellulose nanocrystals and nanofibrils. These nanocellulosic materials are extensively manipulated to provide a rich suite of new materials and platforms for further transformations [81],[82]. This is an important alternative to approaches of full conversion of lignocellulose to biofuels that face challenges arising from the deleterious impact of cellulose crystallinity on enzymatic processing [83].

Figure 6. Potential of mean force (PMF) and aggregation free energy $\Delta G_{agg}$ of cellulose nanofibrils in hemicellulose hydrogels. Parts (a) and (b): Disaggregation by disrupting hydrophilic and hydrophobic contacts, respectively. Parts (c) and (d): PMF along disaggregation pathways (a) and (b), respectively, at glucuronate molar fractions $x=0.0 \text{–} 0.1$ [legend in part (c)]. Grey arrows show PMF change with glucuronate concentration. Parts (e) and (f): $\Delta G_{agg}$ for the hydrophilic and hydrophobic contacts (a) and (b) in hemicellulose hydrogels. Grey dotted line: Sum of the arabinose and acetate curves.
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