Multiscale approach for the construction of equilibrated all-atom models of a poly(ethylene glycol)-based hydrogel

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A multiscale modeling approach is presented for the efficient construction of an equilibrated all-atom model of a cross-linked poly(ethylene glycol) (PEG)-based hydrogel using the all-atom polymer consistent force field (PCFF). The final equilibrated all-atom model was built with a systematic simulation toolset consisting of three consecutive parts: (1) building a global cross-linked PEG-chain network at experimentally determined cross-link density using an on-lattice Monte Carlo method based on the bond fluctuation model, (2) recovering the local molecular structure of the network by transitioning from the lattice model to an off-lattice coarse-grained (CG) model parameterized from PCFF, followed by equilibration using high performance molecular dynamics methods, and (3) recovering the atomistic structure of the network by reverse mapping from the equilibrated CG structure, hydrating the structure with explicitly represented water, followed by final equilibration using PCFF parameterization. The developed three-stage modeling approach has application to a wide range of other complex macromolecular hydrogel systems, including the integration of peptide, protein, and/or drug molecules as side-chains within the hydrogel network for the incorporation of bioactivity for tissue engineering, regenerative medicine, and drug delivery applications.

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I. INTRODUCTION

Polymer hydrogels that consist of a photopolymerized poly(ethylene glycol) (PEG)-based A-B copolymer network are important materials for tissue engineering, regenerative medicine, and drug delivery applications due to properties such as resistance to protein adsorption and nonimmunogenicity, as well as the ability to incorporate bioactive molecules within the hydrogel network.^{1,2} They also provide a highly hydrated environment similar to soft tissues that allows rapid diffusion of nutrients and cellular waste through the porous network for cell viability.^{3–5} In recent applications, these hydrogels have been covalently tethered with bioactive peptides as side chains to mimic the biological activity provided by the extracellular matrix or growth factors, thus providing the potential for cell signaling to mediate a desired biological response.^{6–10}

In order for these materials to function as desired, it is essential that the bioactive agents contained within the hydrogel matrix be presented in a manner that provides for their accessibility and structural integrity for cell-receptor binding. While bioactivity can be experimentally probed by an appropriate set of assays, experimental methods alone are quite limited in terms of their ability to interpret the molecular basis for measured differences in bioactivity for different hydrogel

compositions and designs. Due to this limitation, bioactive hydrogel systems can only be designed at this time by trial-and-error; typically by the application of high-throughput methods.^{11,12} However, because the design space for these complex materials is effectively infinitely large, such trial-and-error approaches still have very limited potential to identify optimal hydrogel designs, thus, in reality, still being rather inefficient. This problem can be surmounted by the development of methods that provide the ability to accurately represent and visualize a hydrogel's molecular structure and assess the presentation of tethered bioactive segments. These abilities can best be provided by the development and validation of molecular modeling methods that are specifically designed for the simulation of these types of materials.

A number of molecular modeling studies on cross-linked polymer networks have been reported over the past couple of decades at both all-atom and coarse-grained (CG) levels.^{13–40} Numerical schemes have also been developed specifically for PEG-based systems; examples include studies of the conformation and hydrodynamics of PEG,²⁸ the interfacial properties of PEG surfactant/water,^{30–32} PEG-contained proton exchange membranes,²² PEG-lipid systems,²⁹ and the development of kinetic models to predict growth, cross-link density profiles, and the level of ligand incorporation for PEG hydrogels.³³ Molecular simulations have also been recently conducted to study the behavior of an individual peptide-polymer

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conjugated chain to examine the influence of the polymer backbone on the conformation of a tethered peptide chain.^{34,35} Most of the recent CG simulations^{19–23,28,31,33,36–40} for PEG-based systems have been carried out using the MARTINI CG force field method,^{41,42} with the CG parameters developed by mapping from the results of atomic simulations based on class I force fields, such as CHARMM,^{28,33} GROMACS,³⁶ and optimized potentials for liquid simulations.^{37,38} In contrast, the all-atom polymer consistent force field (PCFF),^{43–46} which is a class II force field, has been specifically parameterized for the simulation of synthetic polymeric materials, and may provide coverage of polymer functional groups that are not presently available in many of the class I force fields. To our knowledge, no CG models have yet been developed based on PCFF for PEG-based systems in aqueous solution.

Moreover, while previous molecular modeling studies have been reported for polymer hydrogels using all-atom models,^{13–18} CG models,^{19–23,28,31,33,36–40} and lattice models,^{24–27} each of these individual methods has its own unique limitations. As an approach to overcoming the limitations of each individual method, composite modeling schemes have been devised to bridge models at different levels in order to generate well-relaxed atomistic models. The representative multiscale methods include the method of mapping and reverse mapping between atomistic models and high-coordination second nearest-neighbor diamond lattices^{47,48} and face-centered-cubic lattices.^{49–52}

In the present work, we combine lattice, CG, and atomistic simulation methods together in a synergistic manner by using off-lattice CG modeling as an intermediate stage to bridge between a lattice model and a fully atomistic model as a critical step to efficiently equilibrate this type of complex crosslinked macromolecular system. We demonstrate this approach in preparation for the subsequent extension of these methods to produce all-atom models of peptide-functionalized PEG-based A-B copolymer hydrogels. Accordingly, in this paper, we present an overview of our combined methods with a focus on the development and validation of the CG parameters that are required to efficiently and accurately produce all-atom models of bioactive hydrogel networks based on all-atom PCFF parameterization.^{43–46}

II. MATERIALS

Figure 1 presents the two types of cross-linkable chain segments (A and B) that form the PEG-based A-B copolymer

hydrogel. Experimentally, the three-dimensional (3D) hydrogel network is formed by a free-radical photopolymerization process, during which each end of a cross-linker can be linked to at most two ends of other cross-linkers. The pendant side-chains (R) in cross-linker A act as functional groups that can be used to link bioactive molecules within the hydrogel network, such as peptide sequences, proteins, and/or drugs depending on the intended application.

III. METHODS FOR CONSTRUCTION OF A PEG-BASED HYDROGEL MODEL

All simulations were conducted using a modeling toolset consisting of three consecutive parts. (1) A CG model of the network structure of the PEG-hydrogel was first generated with limited parameter constraints to match the experimentally determined cross-link density using an efficient on-lattice Monte Carlo (MC) method based on the bond fluctuation model (BFM).⁵³ (2) The resulting cross-linked polymer network was then moved off-lattice, PCFF-derived CG parameters were developed and applied, and the cross-linked CG network was equilibrated using the “Temperature Intervals with Global Exchange of Replicas, version 2” (TIGER2) advanced sampling method.^{54–58} Finally, the complete atomistic structure of the PEG-based hydrogel network was obtained by reverse mapping the equilibrated CG model to an all-atom model followed by adding explicit hydration and final further equilibration using molecular dynamics (MD), thus providing an all-atom representation of an equilibrated PEG-based hydrogel network.

A. On-lattice BFM Monte-Carlo method

The formation of a cross-linked polymer network is typically modeled as a collision process in which cross-linking happens when two linkable sites meet, as illustrated in Fig. 2. MD methods using all-atom models, or even CG models, are computationally costly in forming a polymer network because of the slow diffusion of polymer chains in the system. In comparison, the much more efficient 3D BFM method has been successfully used to describe the formation of percolating networks and the dynamics of polymer networks, with its predictions shown to compare well with experimental data.^{21,22,59–66} Moreover, BFM has been proven to be an efficient method to work with branched polymers,^{67–69} thus

FIG. 1. Structures of cross-linkers A and B forming the PEG-based A-B copolymer network.

FIG. 2. Schematic description of the formation of an A-B copolymer network using the BFM simulation on a cubic lattice. One chain end can be cross-linked with two other chain ends if the distance between the chain ends is within a range of 2–3 lattice units. The mechanism of cross-linking in a simulation is consistent to that in an experiment.

indicating its potential application for the development of a cross-linked hydrogel network with pendant side-chains. We therefore selected the BFM MC method to generate the initial structure of our PEG-based hydrogel network. To facilitate the subsequent stage of our three-stage approach, which involved a transition from the lattice model to an off-lattice CG model, each lattice site in the BFM structure was designated to represent a single CG bead. The distance between two successive lattice sites, the angle formed by three successive lattice sites, and the dihedral angle formed by four successive lattice sites were then sampled to generally correspond to the bonds, bond angles, and torsional angles, respectively, of the structure to be subsequently represented by the off-lattice CG model.

In the framework of BFM,⁵³ each monomer occupies eight sites of a unit cell in a simple cubic lattice. Monomers along a chain are connected via one of 108 bond vectors (**B**) within the set

$$\mathbf{B} = P(2, 0, 0) \cup P(2, 1, 0) \cup P(2, 1, 1) \cup P(2, 2, 1) \\ \cup P(3, 0, 0) \cup P(3, 1, 0), \quad (1)$$

where $P(x, y, z)$ is the set of all permutations and sign combinations of $\pm x$, $\pm y$, $\pm z$. The allowable bond length can take any one of the five values, which are obtained as the square root of the sum of the squares of the lattice indices designated in Eq. (1) and there are 87 different bond angles between consecutive bonds.

For the on-lattice moves following the BFM method, a randomly selected point representing an CG monomer unit can jump to one of six nearest lattice neighbors; a permissible jump must just satisfy the excluded-volume constraint to avoid overlap of monomers at the same lattice site and the bond-length constraint to avoid intersections of chain segments. While this type of random-walk process greatly accelerates the generation of the polymer network, it treats the polymer chains as being much more flexible than they actually are, thus resulting in a configuration that can be quite distorted

compared to a realistic network structure. This problem then results in a condition requiring excessive simulation time for relaxing the lattice structure into an equilibrated CG model when the lattice restraint is removed and CG parameters are applied. To overcome this problem and accelerate the equilibration of the network using the CG model after the system is taken off the lattice, we imposed CG potential energy terms for bond angle bending [Eq. (3)] and bond rotation [Eq. (4) in Sec. III B] interactions in the BFM-MC simulation. In sampling, the bond lengths, bond angles and dihedral angles defined by BFM are sampled based on these potentials in order to generate configurations of the lattice chain that are close to their equilibration state for the CG model with the lattice being removed. Basically, such an implementation of the BFM method is similar to that used in the works of Tries *et al.*⁷⁰ and Binder *et al.*,⁷¹ in which the BFM sampling was determined by the bond-stretching and angle-bending interactions and the dihedral-angle-rotation interactions were implicitly contained in the parameterization of stretching and bending interactions. The parameters used in these potentials (presented in Tables III and IV) were fitted by the coarse-graining procedure addressed in Sec. III B for the development of the CG parameters. After the polymer network was generated on the lattice with the BFM method, as a final step for preparing the transition from the lattice to the off-lattice models, the coordinates of the lattice points were scaled by a factor of l_c^*/l_b to more closely represent the bond lengths between the CG beads for the off-lattice network, with $l_c^* \approx 3.66$ Å being the most preferred CG bond length (fitted by the distribution of distance between successive ethylene-oxide monomers) and $l_b \approx 2.62$ being the average bond length in the BFM model. Therefore, a factor of $l_c^*/l_b \approx 1.4$ was used for length rescaling when transitioning from lattice model to off-lattice CG model.

B. Coarse-grained parameterization

As noted above, the CG force field parameters for the PEG-based hydrogel network were developed based on PCFF.^{43–46}

FIG. 3. Scheme to build CG models from the atomic models of the network composed of cross-linkers A and B. Without considering the pendant side chain R in a simulation, there are four type of bead, labeled as *a*, *b*, *c*, and *d*.

Figure 3 presents the coarse-graining strategy that we used for the hydrogel network, which was composed of cross-linkers A and B. The mapping point for each bead was taken as its center of mass. There are four types of beads, labeled as *a*, *b*, *c*, and *d* (Table I), six types of bonds (Table II), eight types of bond angles (Table III), and 13 types of dihedral angles (Table IV).

TABLE I. Four types of CG beads and their associated PCFF parameters for the van der Waals interactions in the CG model of the PEG-based A-B copolymer network shown in Fig. 3. The parameters are defined in Eqs. (5) and (9).

Bead type	All-atom representation	σ (Å)	ε (kcal/mol)
a	$\begin{array}{c} \text{H} \quad \text{H} \\ \quad \\ -\text{C}-\text{C}- \\ \quad \\ \text{H} \quad \text{H} \end{array}$	4.500	0.2610
b	$\begin{array}{c} \text{O} \quad \text{H} \\ \quad \\ -\text{C}-\text{O}-\text{C}- \\ \quad \\ \text{H} \quad \text{H} \end{array}$	3.700	0.1321
c	$\begin{array}{c} \text{H} \quad \text{H} \\ \quad \\ -\text{C}-\text{O}-\text{C}- \\ \quad \\ \text{H} \quad \text{H} \end{array}$	4.600	0.0891
d	$\begin{array}{c} \text{O} \quad \text{H} \quad \text{H} \\ \quad \quad \\ -\text{C}-\text{N}-\text{C}- \\ \quad \quad \\ \text{H} \quad \text{H} \quad \text{H} \end{array}$	4.100	0.1438

The potential terms that needed to be parameterized included bonded terms for bond stretching (E_{stretch}), bending (E_{bend}), and rotation (E_{torsion}), and a nonbonded term represented by van der Waals (vdW) interactions (E_{vdW}). The electrostatic interactions between nonbonded CG beads were ignored since all beads are charge neutral. For each term, CG parameters, which included implicit hydration effects, were derived using the iterative Boltzmann inversion of the corresponding atomistic distribution functions obtained from all-atom MD simulations of 4-mer segments of each of the A and B chains immersed in explicit water using the PCFF TIP3P water model.^{72,73} During the iterative procedure for a particular distribution, the rest of the potentials were kept constant. In dense systems, individual distributions usually depend on the full set

TABLE II. Bond types and PCFF parameters for the bonding interactions in the CG model of PEG-based A-B copolymer network shown in Fig. 3. The parameters are defined in Eq. (2).

Bond type	l_{c1} (Å)	l_{c2} (Å)	K_{b1} (Å ⁻²)	K_{b2} (Å ⁻²)	K_{b3}
a-a	2.5455	2.6330	18.5595	43.5497	0.7494
a-b	3.0910	3.2905	80.6761	75.5907	0.6261
a-d	3.2467	3.5822	21.8434	21.9448	0.2492
b-c	3.2576	3.5602	12.2349	70.6596	2.0469
b-d	3.3135	3.5753	8.8770	48.2475	0.6436
c-c	3.4712	3.6614	16.8775	45.7797	2.5776

TABLE III. Bond angle types and PCFF parameters for the bond angle bending interactions in the CG model of PEG-based A-B copolymer network shown in Fig. 3. The parameters are defined in Eq. (3).

Angle type	θ_{c1} (deg.)	θ_{c2} (deg.)	$K_{\theta1}$ (rad ⁻²)	$K_{\theta2}$ (rad ⁻²)	$K_{\theta3}$
a-a-a	120.6912	166.8432	6.1232	9.6223	3.8991
a-a-b	102.6105	150.1611	8.0760	24.3978	3.4211
a-a-d	120.9520	159.4411	2.0876	5.8655	1.9651
a-b-c	113.1720	114.7210	11.0733	68.4179	0.3185
a-d-b	117.3801	132.0408	11.7793	23.4969	1.3046
b-c-c	124.9600	122.7700	11.1141	6.4670	3.8886
c-b-d	125.2903	125.2917	5.7240	11.5270	0.9508
c-c-c	139.9503	144.9832	2.9981	3.0469	0.0958

of potentials through higher-order correlations, requiring that individual potentials must be readjusted after other interactions are changed. In practice, the iteration is usually started with the potentials that are least affected by the changes of others. According to the suggestion of Reith *et al.*,⁷⁴ the potential terms were therefore optimized in the order of their relative strength, with parameterization systematically developed in the order of $E_{\text{stretch}} \rightarrow E_{\text{bend}} \rightarrow E_{\text{vdW}} \rightarrow E_{\text{torsion}}$.

Following our previous approach,^{56–58} the probability distributions of bond lengths and bond angles were fitted by a double Gaussian function, which were then Boltzmann-inverted to provide the potential equations of bond stretching and bond-angle bending. In this way, the bond stretching and angle bending potentials were computed by

$$E_{\text{stretch}}(l) = k_B T \left\{ K_{b1} (l - l_{c1})^2 - \ln [1 + K_{b3} \exp [K_{b1} (l - l_{c1})^2 - K_{b2} (l - l_{c2})^2]] \right\}, \quad (2)$$

$$E_{\text{bend}}(\theta) = k_B T \left\{ K_{\theta1} (\theta - \theta_{c1})^2 - \ln [1 + K_{\theta3} \exp [K_{\theta1} (\theta - \theta_{c1})^2 - K_{\theta2} (\theta - \theta_{c2})^2]] \right\}, \quad (3)$$

TABLE IV. Dihedral angle types and PCFF parameters for the torsional interactions in the CG model of PEG-based A-B copolymer network shown in Fig. 3. The parameters are defined in Eq. (4).

Dihedral type	K_1 (kcal/mol)	K_2 (kcal/mol)	K_3 (kcal/mol)	δ_1	δ_2	δ_3
a-a-a-a	-0.7100	0.2300	0.0300	0	0	0
a-a-a-b	0.0500	0.0700	-0.0100	0	0	0
a-a-a-d	0.0000	0.0000	-0.0600	0	0	0
a-a-b-c	-0.7000	0.1500	0.0000	0	0	0
a-a-d-b	-0.0400	-0.0400	0.0200	0	0	0
a-b-c-c	0.6000	0.3100	-0.0700	0	0	0
a-d-b-c	0.5500	-0.1800	-0.0600	0	0	0
b-a-a-b	0.2200	0.0400	0.0500	0	0	0
b-a-a-d	-0.4000	0.4000	0.4800	π	0	0
b-c-c-c	-0.2000	-0.0200	0.0900	0	0	0
c-c-c-c	-0.1050	0.0300	-0.1000	π	0	0
d-a-a-d	0.0500	0.0300	0.0300	0	0	0
d-b-c-c	0.2300	0.1300	-0.0100	0	0	0

where l and θ are bond length and angle, respectively; k_B and T are the Boltzmann's constant and temperature, respectively; l_{c1} , l_{c2} , l_{c3} , K_{b1} , K_{b2} , and K_{b3} are a set of parameters obtained from the fitting of the bond-length distributions, and θ_{c1} , θ_{c2} , θ_{c3} , $K_{\theta1}$, $K_{\theta2}$, and $K_{\theta3}$ are a set of parameters obtained from the fitting of the bond-angle distributions. The torsional potential was calculated by a threefold Fourier progression formula, i.e.,

$$E_{\text{torsion}}(\phi) = \sum_{n=1}^3 K_n [1 + \cos(n\phi - \delta_n)], \quad (4)$$

where ϕ is the dihedral angle, and K_n and δ_n are force constants and phase angles, respectively.

Following these methods, we constructed atomistic models of the aqueous solutions of the thirteen types of conformers shown in Table IV using PCFF parameterization. Each solution contained one conformer type consisting of the equivalent four CG bead segments capped with methyl groups at each end. A 30-nanosecond (ns) MD simulation was conducted for each modeled system in a cubic box with dimensions $24 \times 24 \times 24 \text{ \AA}^3$. Periodic boundary conditions were applied in all dimensions. The resulting probability distribution plots for each bond type were then used along with Eqs. (2)–(4) for the fitting of the bonded CG parameters.

The nonbonded vdW interactions were represented by the Lennard-Jones 9–6 potential form that is used in the PCFF force field^{43–46}

$$E_{\text{vdW}} = \varepsilon_{ij} \left[2 \left(\frac{\sigma_{ij}}{r_{ij}} \right)^9 - 3 \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right], \quad (5)$$

where ε_{ij} is the depth of the potential well, σ_{ij} is the vdW radius that corresponds to r_{ij} when E_{vdW} is at its minimum value (i.e., $-\varepsilon_{ij}$), and r_{ij} is the distance between a pair of CG beads. The parameterization of the vdW interactions was conducted by an inverted Boltzmann method⁷⁵ in which a numerical potential was determined iteratively by matching the radial distribution functions (RDF) obtained from CG and atomistic models for each type of CG bead unit. The chain segment packing, as represented by the RDF, was then calculated from the probability to find a pair of intermolecular sites within a given distance “ dr ” by

$$g(r) = \frac{\langle n(r) \rangle}{4\pi r^2 dr \rho}, \quad (6)$$

where $\langle n(r) \rangle$ is the average number of intermolecular atom pairs at distance r and ρ is the bulk number density. The vdW potential between nonbonded CG beads was then calculated from the potential of mean force, $E_0(r)$, corresponding to the Boltzmann inversion of the $g_0(r)_{AA}$ obtained from all-atom simulations of the corresponding groups of atoms making up each type of CG bead

$$E_0(r) = -k_B T \ln g_0(r)_{AA}. \quad (7)$$

The actual vdW interaction was determined by an iterative method and tends to converge when the RDF profile calculated by the CG model, $g_i(r)_{CG}$, approaches to $g_0(r)_{AA}$, or

$$E_{i+1}(r) = E_i(r) + k_B T \ln \frac{g_i(r)_{CG}}{g_0(r)_{AA}}. \quad (8)$$

In the method used in previous publications by other groups regarding the coarse graining of polymers,^{76–80} parameterization of the vdW interactions was typically conducted for every pair of CG beads in the system and pairwise tabulated values of the potential were then used in the calculation of nonbonded interactions. This approach is satisfactory for polymers with relatively simple monomeric structures that can be represented with only a few different CG super atoms. However, for more complex polymers containing many types of beads in the CG model, such as what will be needed for the case when side-chain-tethered peptides, proteins, or drug molecules are incorporated within the hydrogel structure, handling vdW parameterization in this manner rapidly becomes very computationally expensive. In the present study, we therefore adopted an approximate but much more efficient approach⁵⁶ to parameterize the vdW interactions. By this approach, low molecular weight compounds that have similar chemical structure as the corresponding super-atom entities defined in the CG model were first identified and then aqueous solutions for each type of compound (20 wt. % solute; approximate composition of experimentally synthesized PEG-based hydrogels) were built at the all-atom level and relaxed at 295 K. The parameters ε_i and σ_i [see Eq. (5)] for same-type CG bead were then obtained by mapping the RDF obtained from the CG model to the RDF of the equivalent atomistic models. For unlike bead pairs, we then used a sixth-order combining rule^{43,46,81} to calculate the off-diagonal parameters

$$\varepsilon_{ij} = 2\sqrt{\varepsilon_i \varepsilon_j} \frac{\sigma_i^3 \sigma_j^3}{\sigma_i^6 + \sigma_j^6}, \quad \text{and} \quad \sigma_{ij} = \left(\frac{\sigma_i^6 + \sigma_j^6}{2} \right)^{1/6}. \quad (9)$$

This combining scheme greatly reduces the computational cost for nonbonded-interaction parameterization and provides an efficient and tractable approach that can be used to model more complex polymeric systems. We have successfully applied a similar scheme for the generation of CG parameters for the vdW terms in previous simulations of amorphous poly-desaminotyrosyltyrosine ethyl ester-succinate, Poly(methyl methacrylate), and poly(n-butyl methacrylate) systems, with validation provided by comparison with x-ray structure factor plots.^{56,57}

Accordingly, to parameterize the nonbonded vdW interactions for the CG model, four all-atom models in aqueous solutions containing 20 wt. % **a**, **b**, **c**, or **d** type of compounds (see Table I) were built in a $40 \times 40 \times 40 \text{ \AA}^3$ box with periodic boundary conditions. The ends of each compound were capped with hydrogen atoms. MD simulations were conducted for each system for 3.0 ns at 295 K, and the vdW CG parameters were subsequently adjusted to match the RDFs obtained from the corresponding all-atom simulations.

After removing the lattice from the hydrogel network and applying the generated CG parameters, the off-lattice system, which is now represented by a strained CG model, must be equilibrated to establish representative models of the hydrogel structure. For this process, we applied the TIGER2 advanced sampling method.^{54,55} This method has two important characteristics: (1) using multiple replicas sampled at different temperature levels to help the system efficiently escape from local potential-energy minima, and (2) enabling the number of replicas used for this replica exchange simulation to be independent of the size of the molecular system. TIGER2 thus provides an accelerated sampling method that can be used to efficiently equilibrate systems that are too large for the application of conventional simulation techniques, such as standard MD or replica exchange molecular dynamics⁸² methods. The TIGER2 method has been successfully applied in simulations of peptides and proteins in implicit solvent^{54,55} as well as amorphous polymers.^{56–58}

C. All-atom model

To obtain the all-atom model of the hydrogel network, a representative structure from the CG model simulation following equilibration (e.g., the lowest energy state in the last 1000 TIGER2 cycles) was used to reconstitute the atomistic structure using a reverse-mapping technique developed by our group.⁵⁶ To implement this procedure, the atomistic structure is rebuilt for each chain by sequences of successive superposition between adjacent CG beads starting from one end-group of each polymer chain. The atomistic counterparts for each bead are superimposed onto the corresponding CG bead by overlapping their centers of mass; with the orientation of the atomic model generally set to correspond to the starting and ending atom for each chain segment. At the end of this reverse-mapping procedure, energy minimization under constant volume periodic boundary conditions was then performed to relax the global all-atom structure. The system was then hydrated with PCFF TIP3P water^{72,73} and all water molecules located within $2.5 \text{ \AA}$ of a solute atom were then deleted to remove atom–atom overlaps. The whole system was then equilibrated using a final MD simulation to provide an all-atom representation of the hydrogel structure, which can be used for direct evaluation and quantification of the PEG-based hydrogel network's predicted structure and properties.

IV. SIMULATIONS AND PARAMETER VALIDATION

As shown in Fig. 1, cross-linkers A and B mainly contain ethylene oxide segments, which we represent as $(-\text{CH}_2-\text{O}-\text{CH}_2-)$, and which correspond to the predominant type of bead c in the CG model. Therefore, the accuracy of the bonded and nonbonded CG parameters for this type of bead are of critical importance for our simulations. All atom and CG simulations were therefore first carried out to assess the behavior of poly(ethylene oxide) (PEO) or, similarly, PEG chains for parameter validation.

To validate the PCFF and PCFF-based CG model parameters for our PEG-based hydrogel, two independent model

systems were first considered: (1) aqueous solutions of single chains of PEO [$\text{H}-(\text{CH}_2-\text{O}-\text{CH}_2)_{n+1}-\text{H}$, with degree of polymerization $n=9, 18, 27$, and 36], and (2) aqueous solutions of PEG [$\text{HOCH}_2-(\text{CH}_2-\text{O}-\text{CH}_2)_n-\text{CH}_2\text{OH}$, with about 10 and 60 wt. % PEG]. For system (1), CG parameters were assessed by comparing the calculated end-to-end distance and radius-of-gyration of each chain with simulations of all-atom models of the same chain lengths in a manner similar to the analyses performed by Lee *et al.*²⁸ For system (2), structure-factor profiles were calculated from all-atom PCFF simulations for solutions of hydrated PEG chains with two different concentrations and compared to structure-factor profiles obtained by x-ray diffraction measurements for PCFF parameter validation. The methods used for the x-ray diffraction analyses are presented in Sec. IV D.

To validate the CG parameters for beads **a**, **b**, and **d** contained in cross-linkers A and B (Fig. 1) and the actual PEG-based hydrogel network (Fig. 3), we constructed three other independent systems composed of aqueous solutions of single n -alkane chains and cross-linkers A and B represented by both all-atom and CG models. Each of these systems was then equilibrated by MD simulation with the resulting chain conformations characterized by mean-square radius-of-gyration and end-to-end distance. The corresponding all-atom and CG simulation results were then compared to assess how well the CG models for these bead types were able to represent the all-atom behavior.

All simulations were conducted using the CHARMM program^{83,84} with in-house modifications to enable use of PCFF CG parameters.⁵⁶ The simulations were performed using the modified velocity VERLET algorithm (VV2)^{85,86} and Nosé-Hoover equations^{87,88} under constant volume and temperature (NVT) conditions. For systems containing water, the water molecules were represented by the modified TIP3P water model for PCFF.⁷³ Time-steps of 2 and 1 fs were used for simulations using the CG and all-atom models, respectively. For the all-atom simulations, covalent bonds involving hydrogen atoms were constrained using the SHAKE algorithm.⁸⁹ The nonbonded vdW (for both CG and all-atom models) and electrostatic interactions (only for the all-atom model) were treated with a real space cutoff of $14 \text{ \AA}$. The TIGER2 simulations to equilibrate the CG model systems used eight replicas with temperature levels being evenly distributed between 295 and 600 K. Each TIGER2 cycle was represented by a sequence of 2 ps heating, 6 ps sampling at the assigned temperature, and 4 ps quenching and relaxation at 295 K. In all simulations, the all-atom model obtained by reverse mapping from a representative CG structure was energy minimized for 3000 steps using the adopted basis Newton-Raphson method (ABNR).⁸³ Further details of the setup for each part of simulation are addressed in Sec. IV.

A. All-atom models of PEO and PEG

All systems were generated initially on-lattice using the BFM-MC method. The resulting structures were then moved off-lattice, CG parameters were applied, and the CG models were equilibrated with TIGER2. The equilibrated CG

models were then reverse-mapped to generate an all-atom model of each system. The all-atom models were then energy minimized, hydrated with TIP3P water, further equilibrated with MD at 295 K under NVT conditions, and then analyzed.

B. PEO chain in aqueous solution

The simulations for single PEO chains of different chain lengths in aqueous solution were conducted to validate the CG parameters for bead-type **c** (see Table I). The conformational behavior of fully atomistic and CG chains were simulated and the results were compared to the previous reports by Lee *et al.*²⁸ Single PEO chains $\text{H}-(\text{CH}_2-\text{O}-\text{CH}_2)_{n+1}-\text{H}$ with chain length $n=9, 18, 27$, and 36 (labeled as PEO9, PEO18, PEO27, and PEO36, respectively) were generated initially by 10^7 steps of BFM-MC on-lattice sampling. Each chain was then taken off the lattice, CG parameterization was applied, and the system was equilibrated using 1000 cycles of TIGER2 sampling. After TIGER2 equilibration, two different initial configurations were selected for each chain length for reverse-mapping to generate all-atom models of PEO. These chains were then hydrated in a periodic TIP3P water box. The dimensions of the periodic boxes were $38 \times 38 \times 38$, $42 \times 42 \times 42$, $48 \times 48 \times 48$, and $56 \times 56 \times 56 \text{ \AA}^3$ for PEO9, PEO18, PEO27, and PEO36, respectively. Again, for each chain length, two independent MD simulations with different initial configurations were conducted to enhance conformational averaging. Thirty-ns NVT MD simulations were then conducted for each system, with the last 25 ns of each trajectory used for the calculation of the root-mean-square (RMS) end-to-end and radius-of-gyration for comparison between the all-atom and CG results, as well as with the published result of Lee *et al.*²⁸

C. PEG chains in aqueous solution and structure factor calculation

Two aqueous PEG solutions labeled PEGS1 and PEGS2 were generated. Both of them contain $36 \text{ CH}_2\text{OH}-(\text{CH}_2-\text{O}-\text{CH}_2)_{46}-\text{CH}_2\text{OH}$ chains (corresponding to about 2000 molecular weight for each chain). The PEGS1 and PEGS2 chains were initially generated on cubic lattices with dimensions $43 \times 43 \times 43$ and $72 \times 72 \times 72$, respectively. For each system, MC sampling was conducted until all chains, on average, diffused a distance that was five times longer than the radius of gyration of the chain, with the radius-of-gyration values being about 9.3 and 11.1 lattice spacing units for PEGS1 and PEGS2 systems, respectively. The final configuration of each system was taken off the lattice and the coordinates of each lattice site were rescaled by a factor of $l_c^*/l_b = 1.4$ in order to yield the mapping of the off-lattice CG model onto the lattice model (see Sec. III A). After rescaling, CG parameters were applied to the PEGS1 and PEGS2 systems and the systems were energy minimized in periodic boxes with dimensions $60 \times 60 \times 60$ and $100 \times 100 \times 100 \text{ \AA}^3$, respectively. Each minimized structure was then equilibrated with the TIGER2 method for 5000 cycles. After TIGER2

equilibration, the lowest energy state of each system from the last 1000 cycles of the TIGER2 trajectory was chosen for reverse-mapping to build the all-atom model. At the end of the reverse-mapping procedure, the global all-atom structure of each system was energy minimized. The optimized all-atom structures of PEGS1 and PEGS2 were then hydrated in TIP3P water boxes with dimensions $60 \times 60 \times 60$ and $100 \times 100 \times 100 \text{ \AA}^3$, respectively, to form two solutions with contents of PEG being about 60 and 10 wt. %, respectively. The systems were then further equilibrated by MD simulation for 5 ns to relax the local chain-segment packing. Structure factor plots of the final all-atom equilibrated structures were then calculated for comparison with structure factor plots experimentally obtained by x-ray analysis, for matched hydrated PEG-chain systems to validate the PCFF parameters for this system, as described in Sec. IV D. The method for $S(q)$ calculation is addressed in Ref. 58.

D. Experimental determination of structure factor profiles

PEG samples of four different molecular weights were chosen for this study and characterized by x-ray scattering: 1 kDa (Fluka), 2 kDa (Sigma-Aldrich), 35 kDa (Fluka), and 100 kDa (Sigma-Aldrich). These molecular weights were chosen because when these polymers are saturated with water over a 3-h period at room temperature, the wt. % PEG in the hydrated samples decreases as the PEG molecular weight increases, being ~60, 40, 25, and 10 wt. %, respectively. The wt. % PEG in each of these samples was measured by determining the minimum amount of water necessary to dissolve the polymers for the x-ray measurements. For x-ray scattering, the polymer was placed in a 2-mm diameter x-ray quartz capillary, water was added to the capillary, and then data were collected after the crystalline peaks disappeared, confirming that the polymer was fully hydrated with the minimum water required.

X-ray scattering measurements were carried out on the beam line 11-ID-C at the Advanced Photon Source, Argonne National Laboratory, Argonne, IL (USA) as described in an earlier paper.⁵⁸ The structure functions were obtained from the x-ray scattering curves measured from $q = 0.3\text{--}20 \text{ \AA}^{-1}$. The parameter q is the scattering vector defined as $(4\pi \sin\theta)/\lambda$, where 2θ is the scattering angle and λ is the x-ray wavelength ($0.1078 \text{ \AA}$). The observed coherent x-ray scattering intensity, $I_{coh}(q)$, was used to derive the structure function $S(q)$, which is defined as

$$S(q) = \frac{I_{coh}(q) - \sum_i x_i f_i^2(q)}{\left[\sum_i x_i f_i(q) \right]^2}, \quad (10)$$

where x_i and f_i are the atomic fraction and x-ray form factor, respectively, for atomic species i , using the program PDFgetX2 by Qiu *et al.*⁹⁰ These experimental data sets were then used for assessment of the reasonableness of the

structures of the hydrated PEG systems that were predicted from the all-atom simulations, thus providing a means of validating both the all-atom PCFF parameters as well as the developed PCFF-based CG parameters for the ethylene oxide segments of the polymer chains.

E. CG validation of bead types a, b, and d

For the purpose of validating the structural behavior of the remaining beads in our CG model (bead types **a**, **b**, and **d**), we prepared single-chain all-atom models of n-alkanes and cross-linkers A and B in vacuum. Each system was first energy minimized and relaxed using MD at 295 K. Four initial configurations of each system were then randomly selected and dissolved in water, which was represented by PCFF's TIP3P water model⁷³ to generate four independent and uncorrelated systems. Similarly, four uncorrelated all-atom structures were randomly selected from the equilibrated solution of each type of single chain and each was mapped to a CG model based on the CG strategy shown in Fig. 3. Each of these CG systems was then energy minimized, equilibrated with MD at 295 K under NVT conditions and then analyzed.

F. n-Alkane chain in aqueous solution

The simulations for single n-alkane chains of different chain lengths in aqueous solution were conducted to validate the CG parameters for bead-type **a** (see Table I). For these studies, we created both all-atom and CG models of single n-alkane chains with a structure of $\text{H}-(\text{CH}_2-\text{CH}_2)_n-\text{H}$ with $n = 4, 5, 6, 7, 8, 9$, and 10, and the results were compared with each other as well as to the previous reports by Ferguson *et al.*⁹¹ Each atomic chain was generated initially from a fully extended state and energy minimized by 1000 steps of ABNR method⁸³ followed by 5 ns of MD relaxation. To enhance sampling efficiency, four different initial configurations were randomly selected for each chain length after MD equilibration. These chains were then hydrated in a periodic TIP3P water box with dimensions of $32 \times 32 \times 32 \text{ \AA}^3$. After another 1000 steps of ABNR energy minimization, 30-ns NVT MD simulation was then conducted for each system. Similarly, four solvated all-atom structures for each chain length were randomly selected to map onto four different CG models and each was relaxed by a 30-ns NVT MD simulation. The last 25 ns of each trajectory was then used for the calculation of the RMS radius-of-gyration for comparison between the all-atom and CG results as well as with the published result of Ferguson *et al.*⁹¹

G. Cross-linkers A and B in aqueous solution

To validate and optimize the CG parameters related to **a**, **b**, **c**, and **d** types of CG bead, we constructed systems of single cross-linker A and B chains contained 19 and 17 monomer units, respectively, with the number of ethylene oxide units in each monomer unit (n in Fig. 1) being 13. The cross-linkers A and B are represented by **adbc**₁₃**bda** and **abc**₁₃**ba** in the CG model, respectively. For each cross-linker, four

independent simulations with all-atom and CG models were conducted to enhance conformational sampling. In simulations using all-atom model, the cross-linker chains were hydrated in a periodic TIP3P water box with dimensions $45 \times 45 \times 45 \text{ \AA}^3$. For each system, 15-ns NVT MD simulation was conducted after 1000 steps of ABNR energy minimization. At the end, the accumulated simulation time thus reached to 60 ns. The last 10 ns of each trajectory was then used for the calculation of the RMS radius-of-gyration for comparison between the all-atom and CG results.

H. PEG-based A-B copolymer hydrogel network

As the starting point for the construction of the hydrogel network, our initial system contained 64 cross-linker A chains and 64 cross-linker B chains. Each of the A and B chains contained 19 and 17 monomer units, respectively, that were composed of the structures shown in Fig. 1, with the number of ethylene oxide units in each monomer unit (n) being 13. Referring to Figs. 1 and 3 the CG bead representation of the cross-linker A and B monomer units are thus $adbc_{13}bda$ and $abc_{13}ba$, respectively. The A-B copolymer network was built initially on a periodic cubic lattice with dimensions $90 \times 90 \times 40$ lattice units. The cross-linking process was modeled as a result of a collision process between chain ends. If a collision between two free chain ends occurred (i.e., separation distance satisfied the bond length allowed by BFM), a new bond was formed. The cross-linking process was stopped when the fraction of bonded chain ends (i.e., the gel fraction) reached a targeted level of 0.98, which is based on experimental values. Once the cross-linking process finished, the cross-linked network was then taken off the lattice, translated to the CG model in a periodic cube with dimensions $126 \times 126 \times 56 \text{ \AA}^3$, and equilibrated off-lattice by 5500 TIGER2 cycles using the CG force field parameters. To obtain the all-atom model of the hydrogel, a low-energy CG structure from the last 1000 cycles of the TIGER2 simulation was selected and converted to its atomistic structure using the reverse-mapping method. The recovered all-atom structure of the A-B copolymer network was then first energy minimized by 2000 steps using the ABNR method⁸³ and then hydrated with TIP3P water. The entire system represented by the hydrated all-atom model was then further relaxed with MD for 5 ns to equilibrate the hydrated hydrogel network. The final hydrogel contained about 23 wt. % A-B copolymer network including 13 and 10 wt. % cross-linker A and B, respectively.

V. RESULTS AND DISCUSSION

A. Coarse-grain parameterization

Based on the atomistic simulation of the different types of conformers in aqueous solution, the probability distributions of various types of bond lengths, bond angles, and dihedral angles were determined from which the bonded parameters of the CG force field were calculated. The CG model parameters were iteratively adjusted by mapping the CG

parameters to match the all-atom profiles. The mapping results for seven distributions of distances between adjacent super-atom groups obtained from atomistic calculations and corresponding CG calculations are shown in Fig. S1 of the supplementary material,⁹² and the CG model parameters for bond stretching interactions [Eq. (2)] are given in Table II. The mapping results for nine distributions of bond angles between three successive super-atom groups obtained from the atomistic calculations (lines) and corresponding CG calculations (open squares) are shown in Fig. S2 of the supplementary material,⁹² and the CG model parameters for the bending interactions [Eq. (3)] are given in Table III. Lastly, the mapping results for the thirteen distributions of dihedral angles formed by four successive super-atom groups obtained from atomistic calculations and corresponding CG calculations are shown in Fig. S3 of the supplementary material,⁹² and the CG parameters for the torsional interactions [Eq. (4)] are given in Table IV for each type of CG dihedral angle.

The parameterization of the vdW interactions was conducted for 20 wt. % aqueous solutions of the four types of small compounds presented in Table I that have similar atomic structures to the superatom groups in the CG model. Starting from the initial RDF [Eq. (6)] obtained from atomistic calculations, the nonbonded interaction parameters were calculated by the iterative Boltzmann inversion scheme defined by Eqs. (7) and (8). The best mapping of the calculated CG RDF profiles to the all-atom RDF profiles are shown in Fig. S4 of the supplementary material.⁹² For each species, the RDFs from the CG simulations closely match the position and height of the main peaks in the profiles obtained from atomic simulations, with some deviations that are inherently due to the representation of asymmetric groups of individual atoms as spherically symmetric beads.

As clearly indicated by Figs. S1–S4 of the supplementary material,⁹² the distributions of bond length, bond angle, dihedral angle, and radial distribution functions calculated by the CG model reproduced the target distributions calculated by the atomistic model very well.

B. PEO chains in aqueous solution

Lee *et al.*²⁸ developed a PEO CG model based on the MARTINI CG force field.^{41,42} For a single PEO chain $[H-(CH_2-O-CH_2)_{n+1}-H]$ in aqueous solution, their CG calculation results agreed very well with their atomistic calculation results for chain lengths $n=9, 18, 27$, and 36. In our studies, we generated four similar systems of PEO solution (PEO9, PEO18, PEO27, and PEO36) using our three-level approach, and calculated the RMS values of the end-to-end distances and the radius of gyration for each system. Comparisons of these properties were then made between our CG and atomistic models, and with the results obtained by Lee *et al.*²⁸ As presented in Fig. 4, the CG results closely agree with both the atomistic results and the results by Lee *et al.*²⁸ for each chain length of PEO in solution. In addition, the dependence of $\langle R_g \rangle$ calculated by the CG model on chain

FIG. 4. All-atom and CG calculation results of the root-mean-square values of the end-to-end distance, $\langle R_e \rangle$, and radius of gyration, $\langle R_g \rangle$, of PEO chains in solution and the comparison of the present calculation results to the corresponding computer modeling results given by Lee et al. (Ref. 28).

length (N_p) satisfies $\langle R_g \rangle \propto N_p^\nu$ with $\nu = 0.516 \pm 0.003$, which agrees well with the ideal chain behavior of $\nu = 0.5$ for short chains in dilute solution.⁹³ These combined results show that the CG model of the PEO chains is able to accurately represent the behavior of the atomistic models of the PEO chains in water, with the results appropriately reflecting the known physical behavior of polymer chains in solution, thus providing a validation of intrachain behavior for both our CG parameter set and the all-atom PCFF parameters for this type of system.

C. PEG chains in aqueous solution and structure factor profiles

Figure 5 plots the temporal evolutions of potential energy of the sampled baseline temperature level states obtained

FIG. 5. Evolution of the potential energy obtained from PEGS1 and PEGS2 simulations with TIGER2 and CG model of PEG.

from the PEGS1 and PEGS2 simulations using the TIGER2 method and the CG model of PEG. It shows that the potential energy resulting from the TIGER2 sampling method dropped rapidly in a very short period after each simulation started and that the overall potential energies quickly plateaued, indicating the CG structures in the PEGS1 and PEGS2 simulations were well equilibrated.

In addition to validating CG parameterization to adequately represent the structural behavior of the chains in our PEO-based systems, as was addressed in Sec. VB, it is also important to validate the ability of the PCFF parameters to represent the packing arrangements of the atoms within the system. We addressed this issue by comparing the calculated structure factors plots, $S(q)$ vs q , with corresponding x-ray diffraction results for two different concentrations of PEG chains in aqueous solution (10 and 60 wt. % PEG). Similar to RDF, $S(q)$ characterizes the relative packing arrangements of atom pairs in a molecular system. For a system, the total $S(q)$ can be decomposed as a weighted sum of partial contributions, which can be conveniently calculated in modeling.

Figure 6 compares the calculated profiles of $S(q)$ for PEGS1 [60 wt. % PEG, thin line in Fig. 6(a)] and PEGS2 [10 wt. % PEG, thin line in Fig. 6(b)] with x-ray diffraction data of PEGE1 [60 wt. % PEG, thick line in Fig. 6(a)] and PEGE2 [10 wt. % PEG, thick line in Fig. 6(b)]. The location of each peak pertains to a specific structural feature. The simulations are able to detect distinctly different locations of peaks related to the position of the atoms in the PEG chains and in the water of hydration caused by their degree of hydration. Close agreement of both peak locations and relative magnitudes is found between the calculated and experimentally measured profiles over a broad spectrum of q values, thus validating the PCFF parameters, and the CG parameters by extension, for representing the atomistic-level packing of PEG chains in aqueous solution.

For the PEGS1 and PEGS2 simulations, Fig. 6 also presents the partial structure functions calculated from the simulations for specific atom pairs, i.e., PEG carbon–PEG carbon (C–C), PEG carbon–PEG oxygen (C–O^P), PEG carbon–water oxygen (C–O^W), PEG oxygen–PEG oxygen (O^P–O^P), PEG oxygen–water oxygen (O^P–O^W), and water oxygen–water oxygen (O^W–O^W) pairs, with which the contributions of atom pair correlations to the total $S(q)$ are specified. By providing such partial structure functions, the molecular simulations provide a means to obtain insight into the inter- and intramolecular interactions from otherwise difficult-to-interpret experimental $S(q)$ profiles. In the calculated $S(q)$ profile for PEGS1 [Fig. 6(a)], the peaks located at $q = 1.6$ and $5.3 \text{ \AA}^{-1}$ are mainly attributed to C–C and C–O^P correlations, the peak at $9 \text{ \AA}^{-1}$ is mainly due to C–C correlation, with some contributions from C–O^P and O^P–O^P correlations also accounting for the shoulder at $10 \text{ \AA}^{-1}$. The peak located at $q = 2.9 \text{ \AA}^{-1}$ is mainly related to O–O correlations attributed to O^W–O^W, O^P–O^W and O^P–O^P. In the calculated $S(q)$ profile for PEGS2 [Fig. 6(b)], the four peaks located at about $q = 2, 2.9, 5$, and $6.8 \text{ \AA}^{-1}$ are mainly related to the

FIG. 6. Comparison of the structure factor profiles obtained by simulation (PEGS1 and PEGS2) and experiment (PEGE1 and PEGE2) for two PEG solutions: (a) PEGS1 and PEGE1 each containing 60 wt. % PEG, and (b) PEGS2 and PEGE2 each containing 10 wt. % PEG. For each case, the partial structure factors calculated for C–C, C–O^P, C–O^W, O^P–O^P, O^P–O^W, and O^W–O^W atom pairs are presented to indicate the contributions of specific atom pairs to the overall structure factor profile.

O^W–O^W correlations, which significantly increased as the content of water increased. The peak at $9 \text{ \AA}^{-1}$ has contributions from both C–C and C–O^P and O^P–O^P correlations in PEG and the O^W–O^W correlations of water. In addition, the C–O^W correlation also contributes to the peak at $q = 2 \text{ \AA}^{-1}$, and the C–C and C–O^P correlations from PEG at 1.6, 3.8 and $5.3 \text{ \AA}^{-1}$ broaden the peaks located at about $q = 2, 5$ and $6.8 \text{ \AA}^{-1}$.

These results thus show, as expected, that for PEGS1, which had more PEG than water, the total $S(q)$ is dominated by the C–C, C–O^P and O^P–O^P correlations from PEG, whereas for PEGS2, which had more water than PEG, the total $S(q)$ is dominated by the O^W–O^W correlation from water. The $S(q)$ profile of PEGS1 presents four major peaks at about 1.6, 2.9, 5.3 and $9 \text{ \AA}^{-1}$, whereas the PEGS2 profile presents five major peaks at about 2, 2.9, 5, 6.8, and $9 \text{ \AA}^{-1}$. When the two profiles are compared, the significant changes of magnitude of peaks at 2.9 and $6.8 \text{ \AA}^{-1}$ and the shift in the positions of peaks from $1.6 \text{ \AA}^{-1}$ (PEGS1) to $2 \text{ \AA}^{-1}$ (PEGS2) and from $5.3 \text{ \AA}^{-1}$ (PEGS1) to $5 \text{ \AA}^{-1}$ (PEGS2) can be taken as clearly identifiable signatures of the dissolution of PEG at

different concentrations. In addition, comparison of the $S(q)$ profiles of highly hydrated PEG [top PEGS2 profile of Fig. 6(b)] and bulk water (bottom O^W–O^W profile of Fig. 6) shows that the peak at $2.9 \text{ \AA}^{-1}$, which has contributions only from O^W–O^W interactions, remains largely unaffected. There are also other significant differences between the two $S(q)$ plots: the $7 \text{ \AA}^{-1}$ peak in the bulk water is more intense than that in the PEGS2, and the 2.2 and $9.4 \text{ \AA}^{-1}$ peaks in the bulk water shift to lower q values of about 2 and $9 \text{ \AA}^{-1}$ in the PEGS2 $S(q)$. These differences can be attributed to the 1.6 and $9 \text{ \AA}^{-1}$ peaks, and the absence of any $7 \text{ \AA}^{-1}$ contribution from C–C, C–O^P, and O^P–O^P interactions in PEG [Fig. 6(b)]. The $S(q)$ analyses of these peaks thus provide insights into the interatomic interactions between the PEG chain and water molecules.

D. n-Alkanes in aqueous solution

Figure 7 presents the atomic and CG simulation results of mean-squared radius of gyration ($\langle R_g^2 \rangle$) for n-alkane chains of various chain length in aqueous solution, along with the

FIG. 7. All-atom and CG calculation results of the root-mean-square values of radius of gyration, $\langle R_g \rangle$, of n-alkane chains in solution and the comparison of the present calculation results to the corresponding modeling results given by Ferguson *et al.* (Ref. 91).

corresponding MD simulation results given by Ferguson *et al.*⁹¹ The calculations of $\langle R_g \rangle$ based on the atomic and CG models are consistent with the results given by Ferguson *et al.*⁹¹ up to n-icosane (i.e., C₂₀). No indication of hydrophobic collapse in size of the n-alkane chains shorter than C₂₀ was observed. The excellent agreement among the atomic and CG simulation results and the results given by Ferguson *et al.*⁹¹ indicates that the developed CG parameters for vdW interactions of type **a** bead, **a-a** bonding, **a-a-a** bending, and **a-a-a-a** rotation interactions are able to accurately represent the conformation of short n-alkane chains.

E. Cross-linkers A and B in aqueous solutions

There are no available published results for comparison for aqueous solutions of the A and B cross-linker chains. To further validate and optimize the developed CG parameters, we conducted MD simulations based on all-atom and CG models of each solution and compared the chain conformation characterized by RMS end-to-end distance and radius of gyration. As presented in Table V, the CG results closely agree with the atomistic results for each cross-linker in solution, indicating that the developed CG model is able to

accurately describe the atomistic chain conformations of both cross-linkers A and B.

F. Construction of PEG-based A-B copolymer hydrogel

Based on the validated CG model, we applied the three-stage simulation toolset to generate and equilibrate all-atom models of a cross-linked PEG-based A-B copolymer hydrogel. Figure 8 presents four snapshots of the system at each step of its development. Step (A) shows the cross-linked A-B copolymer network that was generated with BFM on a periodic cubic lattice. Step (B) shows the CG structure of the network after it was moved off the lattice and equilibrated using TIGER2. Step (C) shows the all-atom structure of the network that was generated by reverse-mapping the lowest-energy-state structure of the system selected from the last 1000 TIGER2 cycles. Step (D) shows the final hydrated and equilibrated all-atom structure of the A-B copolymer hydrogel network.

The purpose of the current work was to develop and validate the methodology and CG model for efficiently constructing the atomic structure of the PEG-based hydrogel. Further work is underway at this time to incorporate tethered peptides into the hydrogel network, with subsequent simulations conducted to predict peptide structure and accessibility at the hydrogel surface as required for cell-receptor binding and/or drug delivery applications.

VI. CONCLUSIONS

The construction and equilibration of the atomic structure of polymer hydrogels in computer simulation using conventional all-atom MD methods are prohibitively expensive in both time and computational resources. To overcome this problem, a three-level multiscale approach has been specifically developed and applied to efficiently construct all-atom models of a cross-linked PEG-based A-B copolymer hydrogel using PCFF parameterization. The lattice BFM MC method enables the fast generation of the cross-linked copolymer network; the CG model which is a key part of the toolset incorporates solvation effects implicitly and bridges the lattice model and the all-atom model of the hydrogel network; the application of the TIGER2 high performance sampling method enables the efficient equilibration of the system.

Preliminary modeling studies characterizing the structural behavior of PEO, PEG, n-alkane, and the cross-linker A and B chains in aqueous solution showed that the chain behavior represented by the CG models were each found to closely

TABLE V. Comparison of all-atom and CG calculation results of the root-mean-square values of the end-to-end distance and radius of gyration of single cross-linker A and B chains in solution.

Type of cross-linker	Root-mean-square of end-to-end distance (Å)		Root-mean-square of radius of gyration (Å)	
	Atomistic model	CG model	Atomistic model	CG model
A	20.8610 ± 0.2550	21.0260 ± 0.3260	8.7950 ± 0.0840	8.9500 ± 0.1140
B	18.3950 ± 0.2440	19.1850 ± 0.2830	8.3250 ± 0.0800	8.5600 ± 0.1010

FIG. 8. Schematic description of the procedure of building the PEG-based A-B copolymer hydrogel. (a) The A-B copolymer network is initially constructed in a BFM simulation on a cubic lattice; (b) the generated network structure is moved off the lattice and equilibrated in a TIGER2 simulation with the developed CG parameters; (c) an all-atom structure is generated by the reverse-mapping method from the equilibrated CG structure followed by further energy optimization; and (d) the all-atom structure is hydrated with explicit TIP3P water (shown as red spheres) and finally equilibrated by further MD simulation. The plots were created by the VMD program (Ref. 94).

represent the all-atom behavior as well as provide close agreement with previous published results.^{28,91} Furthermore, we were able to validate the all-atom PCFF parameters for this type of system, as well as the derived CG parameters, by comparison with structure-factor plots obtained by x-ray diffraction, with the modeling results providing unique insights regarding how specific molecular associations within the hydrogel network contributed to the various profile peaks. These validation studies also confirmed the effectiveness of both the MC-BFM and TIGER2 advanced sampling methods for system equilibration, as well as the reverse-mapping method for transitioning from the CG to the all-atom representation of the molecular systems.

Based on the successful development of the CG parameterization and implementation of the three-level approach to construct equilibrated all-atom models of the cross-linked PEG-based hydrogel system, future computational efforts will be focused on extending these methods to incorporate bioactivity within the hydrogel by adding peptide sequences as side-chains within the network. If successful, the modeling methods will provide the unique ability to predict and visualize the structure of peptide-conjugated hydrogels at an atomistic level. Most importantly, this will provide a direct means of assessing the bioavailability of the tethered peptides at the hydrogel surface as required for cell-receptor binding, thus providing valuable guidance for system design for bioactivity optimization.

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