

Three-dimensional Molecular Geometry of PEG Hydrogels by an “Expansion-Contraction” Method through Monte Carlo Simulations*

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Abstract Three-dimensional (3-D) coarse-grained Monte Carlo algorithms were used to simulate the conformations of swollen hydrogels formed by copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). The simulation consists of three successive steps including diffusion, cross-linking and relaxation. The cross-linking of multifunctional reaction sites is simulated instantly followed by fast crosslinking. In order to explore the validity of this approach pristine poly(ethylene glycol) (PEG) hydrogels with tri- and tetra-functional reaction sites (G3 and G4 respectively) were prepared and characterized. The data from the simulations were found to be in good agreement with experimental results such as PEG lengths between crosslinks, pore volume and pore radius distribution, indicating the validity of the modeling algorithm. The calculated PEG lengths in G3 and G4 networks are close (≈ 4.6 nm). The 3-D visual topological structure of the hydrogel network suggests that the “ideal” hydrogel is far from cubic, diamond or any well defined structures of regular repeating cells.

Keywords: Monte Carlo; Hydrogel; Molecular geometry; CuAAC.

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INTRODUCTION

Three-dimensional hydrogel networks based on poly(ethylene glycol)s (PEGs) swell readily in water. Because of their excellent biocompatibility, PEG hydrogels are promising candidate ranging from tissue scaffolds^[1] to drug carriers^[2]. Hence the study on the typical 3-dimensional topology of hydrogels is an important objective^[3, 4]. For instance, the physical and mechanical properties of hydrogels mediate their applications through the structure and conformation at the molecular scale. It is obvious that the pores of freeze-dried hydrogels at the micron scale observed under scanning electron microscope (SEM) do not represent that of the actual swollen structures that plausibly should be at nm scale. Due to experimental limitations in the characterization at the molecular level^[5], computer simulations including Monte Carlo (MC) simulations^[6, 7] and molecular dynamics of hydrogels^[8, 9] provide a reasonable alternative approach to explore structure-property relationships.

Conventional hydrogels are typically synthesized by random free radical copolymerization of monomers and their multifunctional cross-linkers^[10]. Computer simulation of these polymeric networks was usually carried out with a defect-free model^[11–14]. Due to a lack of controllable polymerizations and low monomer conversion of

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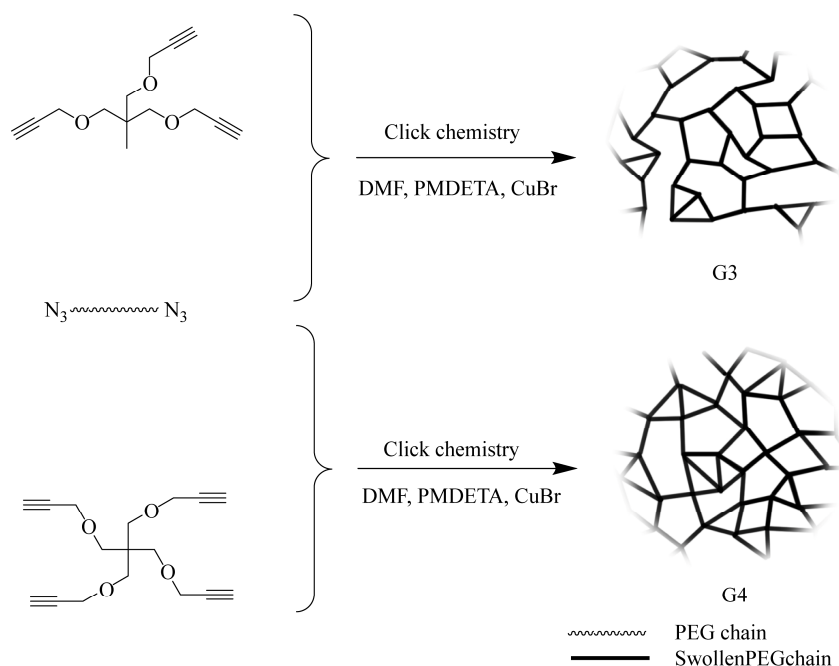
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free-radical copolymerization^[15], it is difficult to model the true molecular structures of these hydrogels, because these hydrogels have poorly controlled molecular structure, high defects and randomly generated cross-links. Hydrogels can also be prepared by coupling reaction of macromolecules^[16], for instance, as reported by Sakai *et al.*^[17].

Recent development of Click chemistry, especially copper(I)-catalyzed azide-alkyne cycloadditions (CuAAC)^[18, 19], has been proved to be a robust tool for the preparation of hydrogels with well-defined molecular structures and improved mechanical properties^[20–24]. PEG based hydrogels based on CuAAC chemistry exhibit high tensile strengths as high as 2.4 MPa^[20] and equilibrium swelling ratios larger than 1000 percent, which make them potentially applicable in artificial organs. These hydrogels exhibit a high gel fraction of up to 0.94 and a fast gelation rate (usually less than 1 min)^[22]. Most importantly, the high conversion and predictable junctions should afford hydrogels having well-defined molecular structures with few defects. The fast gelation time indicates complete and rapid cross-linking. This is quite different from conventional step polymerization based cross-linking.

In this work, we report a novel and effective algorithm to simulate the formation of the molecular conformations of hydrogels. The simulation involves three rapid consecutive steps including diffusion, cross-linking and relaxation. The cross-linking is simulated to occur simultaneously, consistent with the fast gelation under the experimental CuAAC conditions. Hence the model may be expected to be a reasonable representation of the 3-D molecular structure of the experimental hydrogels. The chain lengths, the distribution of polymer chains and pore size in hydrogels, as well as pore volumes are calculated. In order to validate the models, well-defined pristine PEG hydrogels derived from the cross-linkers with 3- and 4-functionalities denoted as G3 and G4, respectively, are synthesized by CuAAC and illustrated in Scheme 1. The data obtained from simulation are comparable with the experimental results. The model developed here could also be applied to end-linked polymer networks from fast step-wise cross-linking.



Scheme 1 Preparation of G3 and G4 via CuAAC

EXPERIMENTAL

Synthesis

Propargyl bromide (80%), PEG ($M_n = 2000$ g/mol), and pentamethyldiethylenetriamine (PMDETA, 99%) were purchased from Aldrich Chemical Co. and were used as received. CuBr (99%), pentaerythritol and sodium azide (99%) were purchased from Shanghai Chemical Reagent Plant. 1,1,1-Tris(hydroxymethyl)ethane was purchased from Acros Organic Co. of Geel, Belgium. The synthesis of tetrakis(2-propynyloxymethyl)methane (TPOM) is the same as described by Xu *et al.*^[22]. The 3-[2,2-bis(prop-2-ynyloximethyl)propyloxy]prop-1-yne (BPY) reagent is the same as described by Gragert^[25] and Schunack^[26] and α,ω -diazido PEG_{2k} (DAP) as used by Fu *et al.*^[27].

G3 and G4 PEG hydrogels were prepared *via* Click chemistry reaction^[22]. As a typical example G3 was prepared by reaction of 0.21 g (0.1 mmol) of DAP, 15.6 mg (0.067 mmol) of BPY, 8.7 mg (0.05 mmol) of PMDETA and 1 mL of DMF that were introduced into a small vial. The vial was degassed with nitrogen for 20 min, and 7.2 mg (0.05 mmol) of CuBr was quickly added under ultrasonic agitation. The gelation point was reached in 1 min, and the reaction was allowed for another 24 h at 60 °C. In the case of G4 hydrogels, 14.4 mg (0.05 mmol) of TPOM was used as the cross-linker.

Characterization

The PEG hydrogels were washed by 5% EDTA aqueous solution to remove the copper catalyst and DMF. Their equilibrium degree of swelling (SR) and equilibrium water content (WC) were determined as follows. The prepared PEG hydrogel was dried at 30 °C for more than 72 h until constant weight recorded as m_{dry} . Then this sample was immersed in deionized water for at least 48 h in order to allow equilibrium swelling conditions. When the weight of the swollen hydrogel reached a constant value, it was recorded as m_{swollen} . Each value was the average of three measurements. SR and WC of hydrogels were calculated by Eqs. (1) and (2), respectively.

$$\text{SR} = \frac{m_{\text{swollen}} - m_{\text{dry}}}{m_{\text{dry}}} \times 100\% \quad (1)$$

$$\text{WC} = \frac{m_{\text{swollen}} - m_{\text{dry}}}{m_{\text{swollen}}} \times 100\% \quad (2)$$

SIMULATION MODEL AND ALGORITHM

A novel three-dimensional (3-D) coarse-grained Monte Carlo algorithm is developed to simulate molecular structures of swollen hydrogels prepared by copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). An ideal polymer network is defect-free where every functional group in both cross-linkers and that of the PEG chains is reacted quantitatively. This assumption is reasonable as “Click chemistry” is known to be quantitative (see Experimental section).

Here, an “off-lattice coarse-grained node-spring model” in 3-D is involved instead of a lattice models because the excluded volume effects tend to be dominant in this case^[28]. The study was concentrated on the network topology and the resulting properties in a well-defined hydrogel prepared by click chemistry. In this coarse-grained model, springs, *i.e.* PEG chains, connect nodes, *i.e.* “generic” cross-linkers, where chemical details are neglected. As the diameter of the nodes is much smaller than the length of the springs (PEG chains), their excluded volumes are assumed to be negligible.

A new overall 3-step strategy to build an ideal network from an “explosion-contraction” MC algorithm is illustrated in Fig. 1. To our knowledge, this is the first example of applying the simulation to hydrogels and it should be applicable widely. First, a diffusion step expands the cross-linkers from a high-density random chain status. This step stops when the nodes have expanded far enough to ensure a pseudo-equilibrium state of randomly distributed nodes *via* a “virtual explosion”. Second, a cross-linking step is allowed to form the network by connecting the nodes statistically and simultaneously to satisfy their reaction stoichiometries. Third, a relaxation step allows the network to reach an energy minimum. The equilibrium distances between nodes are set

smaller than that in the first step to allow a fast conformational contraction of the network *i.e.* relaxation. It is worth pointing out that all units in these simulations are dimensionless and scaled to experimental value by a single parameter after the network is built (see section 4).

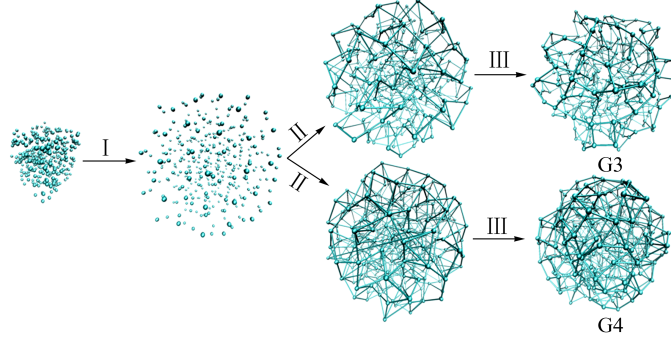


Fig. 1 Overall procedure to build ideal hydrogel networks (I: diffusion, II: cross-linking and III: relaxation) Balls and bonds represent cross-linkers and fully swollen PEG chains, respectively.

At the initial state in the diffusion step, N nodes ($N = 400$ in Fig. 1) are scattered randomly in a $7.2 \times 7.2 \times 7.2$ cubic box. A typical initial state is illustrated in Fig. 1. A Lennard-Jones potential energy is applied to evaluate the interactions between nodes as shown in Eq. (3).

$$U_{\text{diffusion}}(r) = \begin{cases} 4\varepsilon[(\sigma/r)^{12} - (\sigma/r)^6], & r < r_{\text{cut_off}} \\ 0, & r \geq r_{\text{cut_off}} \end{cases} \quad (3)$$

where the σ (the finite distance at which the inter-particle potential is zero), ε (the depth of the potential well), and $r_{\text{cut_off}}$ (the cut-off distance) are arbitrarily defined as 5, 1, and 2σ . This truncated potential is applied to save computational time, as the interactions at $r > r_{\text{cut_off}}$ are insignificant. The parameters are optimized *via* trial and error to achieve a faster convergence and to avoid implausible structures, for instance, nodes too far away.

Every MC move attempt of nodes is accepted according to the standard Metropolis criteria^[29] as shown in Eq. (4).

$$W = \min[1, \exp(-\frac{\Delta E}{k_B T})] \quad (4)$$

where ΔE is the energy change after each MC move, *i.e.* $\Delta E = E_{\text{after}} - E_{\text{before}}$. $k_B T$ is simply set a value of 1.

The rejection ratio of a conventional Metropolis move in this high-density system is high, thus increasing computation time. Hence, a “force based” translational move method is applied, in which direction and distance of the move are calculated based on the resultant force on each randomly selected node according to Eq. (5).

$$\mathbf{D}_{\text{diffusion}} = A \frac{\mathbf{d}}{|\mathbf{d}|^4} \quad (5)$$

where $\mathbf{D}_{\text{diffusion}}$ is the displacement vector, and $\mathbf{d}$ is the distance vector of the selected node and another node that has an interaction with it. The distance of MC move is empirically chosen to be inversely proportional to fourth power of the module of distance vector so that near nodes are easily “pushed away” from each other, resulting in a fast convergence in energy. A is the displacement amplitude that is empirically varied from 0.005 to 0.64 by doubling after every 12.5 Monte Carlo steps (MCS), in order to minimize the energy instability due to the high density at initial steps and obtain a faster convergence at later steps. A MCS is defined as a process in which every node on average finishes one move, *i.e.*, one MCS involves N moves of nodes.

A verlet list^[30] is applied to reduce computation time because the direct energy computing process is relatively time-consuming with a time complexity of $O(n^2)$. This diffusion process is arbitrarily stopped after 100 MCS, which is sufficient for nodes to move to the position where most distances among them are larger than 2 (Fig. S1(A)). This distance is selected as the equilibrium distance between nodes after connection, *i.e.* l_0 (see below). The systematic energy is recorded during every MCS, and reaches a steady minimum after 70 MCSs, indicating an equilibrium of the nodes, as is shown in Fig. S2(A).

Inspired by the fast gelation of CuAAC, cross-linking is performed simultaneously among all nodes under a “node with low functionality connecting first” rule explicitly illustrated in Fig. 2. Here, the connecting is randomly started from a node (denoted as A) that has the lowest functionality in the system. Then, a search is performed to find the unsaturated (functionality < 3 and 4 for G3 and G4, respectively) node (denoted as B) that has a distance closest to l_0 (the relaxation length) with A. The connection is conducted between node A and B. The cross-linking is stopped when every cross-linker reached the functionalities of 3 and 4 for the cases of G3 and G4, respectively. Different from others^[31, 32] work, a low-functionality priority was applied here, which allows the cross-linking to be performed simultaneously. Thus, the simulation not only consists with the formation mechanism of CuAAC, but also reduces computer’s central processing unit (CPU) time substantially.

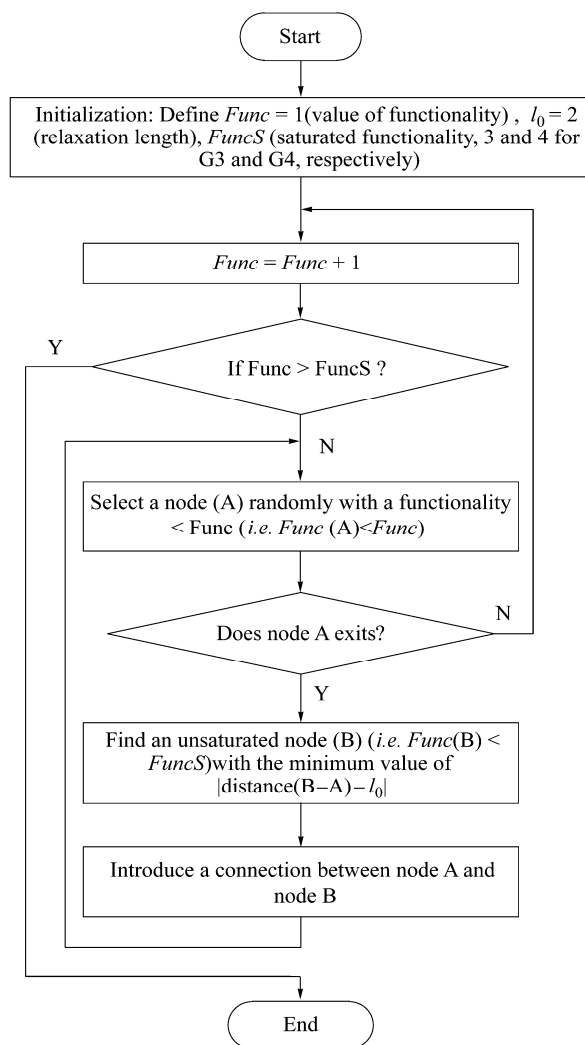


Fig. 2 Flow chart of the cross-linking step

In an ideal swollen hydrogel, all PEG chains are in the same environment and have a same chain length. When the cross-linking step is ended, the lengths of the springs between nodes showed a wide distribution and thus a high potential energy. In order to obtain the energy minimum of the network, the relaxation step is performed, which allows springs to stretch and contract. The relaxation step is carried out based on Hooke's law as shown in Eq. (6).

$$U_{\text{relaxation}} = \sum_{m=1}^{N_{\text{spring}}} \frac{k_{\text{spring}}}{2} (l_{m,\text{spring}} - l_0)^2 \quad (6)$$

where N is the total number of springs in the network, and l_0 , set as 2 (see below), is the unperturbed equilibrium spring length. k_{spring} is the Hookean constant which is arbitrarily defined as 100. If the Hookean constant were to be much larger, the movement of nodes would be too computationally demanding. However, if it were much smaller, the system was demonstrated to become unstable and showed pronounced oscillations.

For each MC move in relaxation, the displacement is calculated based on the resultant force on the randomly selected node as shown in Eq. (7).

$$\mathbf{D}_{\text{relaxation}} = B \mathbf{F} \quad (7)$$

where $\mathbf{D}_{\text{relaxation}}$ is the displacement vector. B is the displacement amplitude, and $\mathbf{F}$, vector of the resultant force of the selected node. The same Metropolis acceptance rule as Eq. (2) is applied here to decide whether the new move is accepted or not. The relaxation procedure requires a computation time of about 750 MCS, which takes about 20 min on a desktop personal computer equipped with an i5 quad-core CPU. The energy change in diffusion and relaxation of each MCS is recorded and shown in Fig. S2(B). According to the energy profile, the systematic energy has reached a steady minimum and the distances between nodes lead to a value of l_0 (Fig. S1(B)) after 500 MCSs, indicating equilibrium of the nodes consistent with our choice of the parameter sets. Further verification is done by analyzing the pair distribution function (PDF) for three structures (G0 for structure before relaxation) generated from one random seed, shown in Fig. S3. After relaxation, the springs have stretched to the same length with errors less than 0.1%. This simplification may be justified according to the narrow molar mass distribution (PDI = 1.05) of α,ω -diazido PEG_{2k} (DAP), shown in Fig. S4.

To calculate the statistical properties within the model, networks are isolated in spherical boxes (rather than cubic ones) in order to minimize boundary effect and maximize the use of nodes and springs in globular networks. All the results used in the following discussions are averaged from 20 runs of MC program. The programs were coded by C language. The codes of the three steps are included in the Supporting Information.

RESULTS AND DISCUSSION

Three hydrogels of each G3 and G4 were synthesized under the same conditions, The data are the average of 3 measurements of each group of hydrogels to minimize statistical errors. G3 hydrogels have a higher SR of (1412% ± 28%) than G4 of (808% ± 65%) in water. Water content (WC) of G3 and G4 hydrogels are (93.4% ± 0.1%) and (89.0% ± 0.8%), respectively. The standard deviation of swelling data is relatively small, suggesting an excellent synthetic repeatability typical for Click chemistry. The higher SR and WC in G3 indicate that G3 has larger pore volumes than G4^[33, 34]. This is intuitively clear and should be consistent with principles of step polymerization^[35].

Parameterization and Validity of the Model

Here, computation model is built based on a same set of dimensionless parameters (given in Table 1) for G3 and G4 hydrogels (instead of the experimental data). After simulation the calculated data was parameterized with experimental results.

Table 1. Parameters in MC modeling

ε	σ	A	l_0	k_{chain}	B
1	5	0.005–0.64 ^a	2	100	0.05

^a The variable A is doubled every 12.5 MCS

Given the quantitative conversion of click chemistry, the density of cross-linkers and PEG chains in a hydrogel is calculated from the relative molar amounts of reagents by Eq. (8).

$$C_{\text{exp_cross(PEG)}} = \frac{n_{\text{exp_cross(PEG)}}}{V_{\text{exp_cross(PEG)}}} \approx \frac{N_A \times m_{\text{exp_cross(PEG)}} / M_{\text{n_cross(PEG)}}}{m_{\text{exp_gel}} / \rho_{\text{H}_2\text{O}}} \quad (8)$$

where N_A is the Avogadro constant, *i.e.* $6.022 \times 10^{23} \text{ mol}^{-1}$. $n_{\text{exp_cross(PEG)}}$ is the number of cross-linker or PEG chain which can be calculated from the molar masses of the experimental precursors, *i.e.* M_n of $2156 \text{ g}\cdot\text{mol}^{-1}$ for DAP, $234 \text{ g}\cdot\text{mol}^{-1}$ for BPY and $288 \text{ g}\cdot\text{mol}^{-1}$ for TPOM, $1 \text{ g}\cdot\text{mL}^{-1}$ was used as the density of the fully swollen hydrogels considering its high water content ($> 89\%$) and the comparable dry PEG density ($\rho_{\text{PEG}} = 1.13 \text{ g}\cdot\text{mL}^{-1}$).

The simulated node density can be simply calculated by Eq. (9).

$$C_{\text{sim_node(spring)}} = \frac{n_{\text{sim_node(spring)}}}{V_{\text{box}}} \quad (9)$$

where $n_{\text{sim_node(spring)}}$ is the number of nodes (or springs) within the spherical box with the volume of V_{box} . When the spherical box is applied, nodes within the box are recorded, while springs are recorded proportionally according to their length percentage in the box. The scales in G3 and G4 models are parameterized based on the experimental density of cross-linkers or PEG chains in the hydrogels. Eq. (10) describes the definition that one unit of dimensionless length in simulation equals $S \text{ nm}$ in a real hydrogel.

$$S = \sqrt[3]{\frac{C_{\text{sim_node(spring)}}}{C_{\text{exp_cross(PEG)}}}} \quad (10)$$

Before parameterization, a spherical box, containing about 90% of the total nodes or springs, is applied and its radius is recorded. The average radii of G3 and G4 are 8.9 and 7.8, respectively. Density fluctuations were investigated for both G3 and G4 models. The statistical densities of nodes (and springs) are plotted as a function the molar fraction of nodes (and springs) against that of the largest spherical box. The data are averaged from 20 generated structures (see Fig. 3). It is found that after cross-linking and equilibrium, G4 network has shrunk to a more dense state than G3. The calculated radial density distribution is narrow from 40% to 90% percent (Fig. 3) of nodes (and springs) in both structures, indicating the homogeneity and self-consistency in both models.

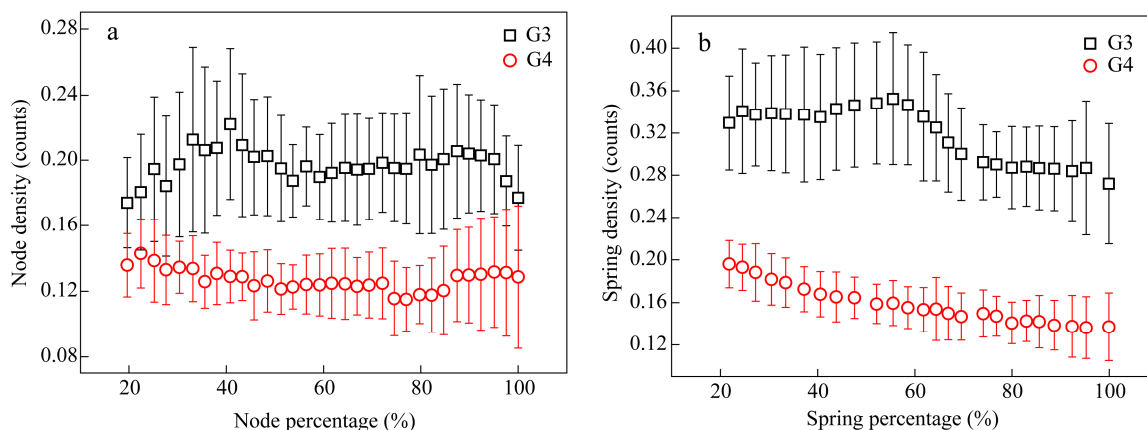


Fig. 3 Density distribution of nodes (a) and springs (b) in simulation averaged from 20 groups of generated samples

Averages of the density ranging from 40% to 100% are applied to parameterize the dimensionless unit by comparing to the experimental density. The scales of the models were determined based on the Eq. (10). The S values were calculated from experimental densities of PEGs and cross-linkers (Table 2). The PEG chain lengths in the models were calculated from S value from an average of 20 structures. As shown in Table 2, the chain

lengths of PEG_{2k} are (4.513 ± 0.085) nm and (4.667 ± 0.129) nm in G3 and G4 swollen hydrogels, respectively. The Flory dimension of PEG_{2k} is $3.45 \text{ nm}^{[36]}$, which can be calculated from $R_F = aN^{3/5}$ (where a is the persistence length of the PEG monomer, $a = 0.35$ nm; N is the number of PEG repeating units, $N = 45$ for PEG_{2k}). Moreover, the chains of PEG_{2k} when closely spaced and bound at one end to a particle surface have length reported as $6.4 \text{ nm}^{[37]}$. Thus the calculated PEG sizes in this work falls in between a free coil and a stretched one.

Table 2. Data after parameterization calculated from cross-linker and PEG chain density

Model	S^a (nm)	S^b (nm)	S^c (nm)	Length of PEG _{2k} (nm)	Average pore radius (nm)
G3	2.22 ± 0.01	2.29 ± 0.02	2.26 ± 0.04	4.51 ± 0.09	3.37 ± 0.06
G4	2.29 ± 0.05	2.37 ± 0.05	2.33 ± 0.07	4.66 ± 0.13	3.14 ± 0.08

^a Calculated from cross-linker density; ^b Calculated from PEG density; ^c Calculated from cross-linker and PEG density and used for later calculation

Pore Size and Distribution

Pore size and distribution are the main concern of the hydrogels. Hydrogels with large pore size exhibit rapid swelling and deswelling properties^[33, 34], which are promising in gastric retention devices^[33] and other medical applications. An algorithm by calculating total volume of ‘spheres’ that can be placed in the networks (Fig. 4), was developed here to analyze the pore of the model. Here, ‘spheres’ are roughly calculated as circumscribed spheres of tetrahedrons with 4 nearest nodes in network. As shown in Table 2, the average calculated pore radii of G3 and G4 are (3.378 ± 0.063) and (3.140 ± 0.087) nm, respectively. The Flory-Rehner equation^[38] can be used to estimate the average molecular weight between two cross-linkers (M_c) and mesh size ξ of the polymer network based on the swelling of the hydrogels at equilibrium in water^[39, 40], as shown in Eqs. (10) and (11).

$$\frac{1}{M_c} = \frac{2}{M} - \frac{\frac{v}{V_1} [\ln(1 - v_{2,s}) + v_{2,s} + \chi v_{2,s}^2]}{[v_{2,s}^{1/3} - \frac{v_{2,s}}{2}]} \quad (10)$$

where $v_{2,s}$ is the volume fraction of polymer in swollen gel (determined as roughly the inverse of the equilibrium swelling ratio), χ is Flory-Huggins parameter for PEG-water, V_1 is the molar volume of swelling agent and M is molecular weight of polymer chains before cross-linking.

$$\xi = v_{2,s}^{-1/3} \left(\frac{2C_n \bar{M}_c}{M_r} \right)^{1/2} l \quad (11)$$

where l is the average value of the bond length between C—C and C—O bonds in the repeat unit of PEG (0.146 nm), C_n is the characteristic ratio ($C_n = 4.0$ for PEG), and M_r is the molecular weight of the repeating unit ($44 \text{ g} \cdot \text{mol}^{-1}$).

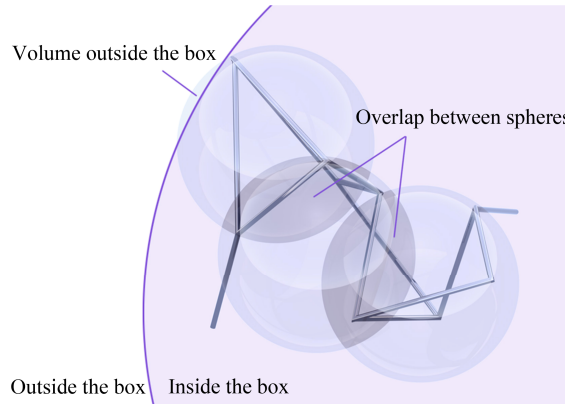


Fig. 4 Illustration of the overlapping of spherical pores and the pores partially outside the box. The large sphere represents box edge, small spheres for pores, and straight lines for springs.

Calculated from this method, the radii of the mesh sizes of G3 and G4 are (2.349 ± 0.028) and (1.870 ± 0.076) , respectively. The pore size from the model is consistent with that calculated by Flory-Rehner equation. In fact, overlapping spheres are inevitable. When conducting the search of circumscribed spheres, the spheres completely outside of the box and duplicated spheres are deleted in advance. Thus the total volume of pores in network is derived as Eq. (12).

$$\sum V_{\text{pore}} = \sum V_{\text{sphere}} - \sum V_{\text{sphere-sphere}} - \sum V_{\text{sphere-box}} \quad (12)$$

where $\sum V_{\text{sphere}}$ is total volume of found circumscribed spheres, $\sum V_{\text{sphere-sphere}}$ is overlap volume among spheres, $\sum V_{\text{sphere-box}}$ is volume that is outside of the box for those spheres partially inside the box and, $\sum V_{\text{sphere-sphere}}$ can be calculated by Eq. (13).

$$\sum V_{\text{sphere-sphere}} = \sum V_{2\text{spheres}} + \sum V_{3\text{spheres}} + \sum V_{4\text{spheres}} \cdots \quad (13)$$

where $\sum V_{2\text{spheres}}$ represents the volume of intersection between two spheres, and so forth. The probability of the overlap among more than 3 spheres is too low to be considered. $\sum V_{3\text{spheres}}$ is calculated by the previous method^[41], and $\sum V_{2\text{spheres}}$ can be calculated by adding up the volume of two spherical caps in the intersection section (Eq. 14).

$$V_{\text{cap}} = \frac{\pi h^2}{3}(3r - h) \quad (14)$$

where r is the spherical radius and h is the height of the “cap”.

Pore volume is then calculated as Eq. (15).

$$P_{\text{pore}} = \frac{\sum V_{\text{pore}}}{V_{\text{box}}} \times 100\% \quad (15)$$

For both G3 and G4 cases, pore volume is calculated from 20 generated networks with a spring density varied from 80% to 90%. The calculated pore volumes are $(85.4\% \pm 2.4\%)$ and $(82.4\% \pm 0.8\%)$ for G3 and G4, respectively. The calculation pore volumes are comparable with experimental WC of G3 $(93.4\% \pm 0.1\%)$ and G4 $(89.0\% \pm 0.8\%)$.

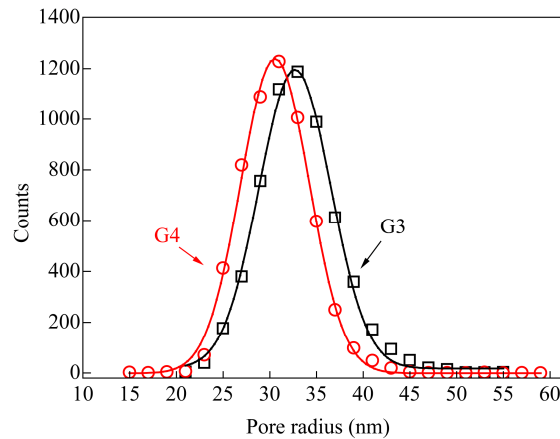


Fig. 5 Pore size distribution of G3 and G4 networks accumulated for 20 groups of samples at 85% radius (Fittings by Gaussian distribution are shown in solid lines.)

Table 2 shows the calculated average pore sizes of G3 and G4 hydrogels averaged from 20 groups of simulated networks. G3 networks have a larger pore fraction and average pore size than those of G4 hydrogel networks, which account for the higher experimental SR in G3 than that in G4. G3 and G4 have a similar

Gaussian distribution in pore size distributions, as depicted in Fig. 5. G3 has a wider distribution of pore radius (half-peak width = 9.152 nm) than that (half-peak width = 8.621 nm) of G4. The experimental pore size can be obtained from the molar mass distribution and is shown in Fig. S5, based on the assumption that in a perfect network lattice, pore radius are proportional to the molar mass and the pore volume is proportional to the cube of molar mass. The experimental pore size is comparable to the calculated one in the model.

Therefore, the pores of ideal networks are not uniform, which is far from “perfect”, previously assumed as the “diamond-like network”^[12, 14, 42].

CONCLUSIONS

In this work a 3-step Monte Carlo method including diffusion, cross-linking and relaxation was developed to simulate the networks topology of swollen well-defined PEG hydrogels prepared by CuAAC. The model was validated by comparing the parameterized length of PEG and pore volume to the experimental data. The average lengths of the PEG chains in G3 and G4 swollen hydrogels were calculated as (4.51 ± 0.09) nm and (4.66 ± 0.13) nm, respectively. Calculated pore volume reproduces the experimental data quite well. The Gaussian distributions of pore sizes in both G3 and G4 networks indicate that even “ideal” hydrogel networks are far from perfect (or homogeneous). Therefore, we suggest that a “perfect” illustration in cubic, diamond or any other regular topology with repeating cells should not be applicable for gels. In summary, MC simulations provide a feasible way to explore polymer hydrogel conformations. Further studies along these lines are in progress.

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