Structure and dynamics of tetra-PEG gel by Brownian dynamics

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We have made coarse-grained model for the tetra-PEG gel and analyzed the gel formation process and the structure of the tetra-PEG gel by using Brownian dynamics simulation. The simulations successfully obtain a reasonable reaction rate with respect to the simulation step. Calculating the number and types of cross-linkings before and after gelation, we found that gelation is caused by monomers with up to three cross-linkings. After gelation, most of the cross-linkings occur in the largest cluster, with cross-linking in the fourth reactive group. By studying mesh structure in the gel after cluster formation, we found the decrease of the size of the loops by cross-linkings. Particularly, loops of size eight were most abundant in our system, which can be one of the reasons for the high strength of the gel.

Key words: gel, Brownian dynamics, cross-linking, network

1. INTRODUCTION

Polymer gel has three-dimensional network structure consisting of polymers. Hydrogel, having flexibility and absorption property, are used in various products such as contact lenses and diapers. Although the gels have these characteristics, application as a structure material has been limited by low strength, due to the micro-inhomogeneities of the three-dimensional structure. When we apply stress on such gel with inhomogeneous network, it will start to break at its weakest part. On the other hand, the cartilage in human body distributes the stress by the layered structure, and has high strength. Various researches are done for making the gels of such high strength. For instance, there is topological gel [1] with sliding cross-links and double network gel [2] with two types of independent networks. These gels have high strength because of their cooperativeness. However, considering the biocompatibility, there is concern over complex processes and toxic residual monomers.

Sakai and coworkers succeeded in making strong gel (up to 9 MPa) by using two types of tetra-polyethylene glycol (tetra-PEG) [3-6]. Moreover, the succinimidyl group formed as a by-product is a citric acid derivative; it can be metabolized easily in the citric acid cycle. Tetra-PEG gel is easy to produce and has high biocompatibility.

For polymer gels such as tetra-PEG gel, direct observation of the gelation process in the experiment is difficult. We construct a coarse-grained model for the gel of tetra-PEG and

perform Brownian dynamics simulation. Based on the results of such simulation, we discuss the gel formation process and the structure of the tetra-PEG gel.

2. SIMULATION MODEL AND METHOD

Since the molecular weight of tetra-PEG is more than 10,000, simulation of full atomic model requires enormous computational time. Thus, we have made a coarse-grained model for the tetra-PEG gel and analyzed the formation process and structure of the gel by using Brownian dynamics simulation, which is a combination of molecular dynamics and Langevin equation with random force. Figure 1 shows the coarse grained model of the tetrahedral monomer consisting of five “particles”, which are four function groups and the center of tetrahedral. We have introduced two types of tetra-PEG, tetrahedron-like monomers, α and β , of the same size. Monomers α and β react with each other; two α -monomers (two β -monomers) do not react with each other.

Using the potentials described below, we perform Brownian dynamics simulations according to Langevin equation,

$$\frac{d^2\mathbf{r}}{dt^2} = -\frac{dU}{d\mathbf{r}} - \zeta\mathbf{v} + \mathbf{R}(t), \quad (2.1)$$

where ζ is viscosity coefficient. The first term on the right-hand side is a force from the potentials, the second term is viscous term, and the third term is random force, satisfying the following equations;

Figure 1. Chemical formula of tetra-PEG (a) and coarse grained model of two tetra-PEG (b). The five particles are the four function groups and center of tetrahedron

$$\langle \mathbf{R}(t) \rangle = 0, \quad (2.2a)$$

$$\langle \mathbf{R}_i(t) \cdot \mathbf{R}_j(t') \rangle = 6\zeta k_B T \delta_{ij} \delta(t - t') \quad (2.2b)$$

where $\langle \dots \rangle$ represents the statistical average and T is absolute temperature, and k_B is Boltzmann constant. Eq. (2.2b) shows the correlation of the random force between particle i at time t and particle j at time t' .

Between different types of monomers between α and β , we use Lennard-Jones potential;

$$U_L(r) = \varepsilon_0 \left\{ \left(\frac{r_0}{r} \right)^{12} - 2 \left(\frac{r_0}{r} \right)^6 \right\}, \quad (2.3)$$

where r is the length between two particles, r_0 is the equilibrium bond length between monomers, and ε_0 is binding energy between monomers at the equilibrium state.

Between same types of monomers, we assume the following repulsive potential.

$$U_{rep} = \varepsilon_0 \left(\frac{r_0}{r} \right)^{12}. \quad (2.4)$$

For the chemical bond in the monomer we use spring potential.

$$U_{bond}(r) = \frac{1}{2} K_{bond} (r - r_0)^2, \quad (2.5)$$

where K_{bond} is the spring constant. When a particle belonging to (α)-monomer and a particle belonging to (β)-monomer are within the distance r_0 , we connect the two particles with a bond with probability 0.5% per step. This probability was chosen, because two particles are in contact for about 20steps, and the experimental probability is about 10% per contact. This

Figure 2. Snapshot after the initial relaxation (a) and at the end of simulation after 5×10^5 steps (b).

potential is switched on in the radius of $r_{cut} = 5.0$ in the unit described later, and once the bond is formed, it cannot be dissociated during the simulation.

We use the angle dependent potential to maintain the tetrahedral bond angle of the monomer. This potential is represented by the following formula.

$$U_{angle}(\theta) = \frac{1}{2} K_{angle} (\cos \theta - \cos \theta_\alpha)^2 \quad (2.6)$$

where K_{angle} is a coefficient representing the strength of the angle potential, and θ is the bond angle. We set $\cos \theta_\alpha$ equal to $-1/3$ for the tetrahedral structure, and we set θ_α equal to π to maintain the bond angle along the straight line.

Finally, we used Tersoff potential [7] to control two particles which have no bonds.

$$V_{ij}(r_{ij}) = f_c(r_{ij}) [f_R(r_{ij}) + b_{ij} f_A(r_{ij})] \quad (2.7a)$$

$$f(r_{ij}) = A_{ij} \exp(-\lambda_{ij} r_{ij}) \quad (2.7b)$$

$$f(r_{ij}) = -B_{ij} \exp(-\mu_{ij} r_{ij}) \quad (2.7c)$$

Figure 3. Schematic of configurations with periodic boundary condition, (a), (b) and (c) become (a'), (b'), (c'), respectively. (a) and (b) are not gel, (c) is gel, because the structure is percolation in both x and y directions.

$$f_c(r_{ij}) = \begin{cases} 1 & (r_{ij} < R_{ij}) \\ \frac{1}{2} + \frac{1}{2} \cos \left[\pi \frac{r_{ij} - R_{ij}}{S_{ij} - R_{ij}} \right] & (R_{ij} < r_{ij} < S_{ij}) \\ 0 & (S_{ij} < r_{ij}) \end{cases} \quad (2.7d)$$

where R_{ij} is bond length, S_{ij} is cutoff radius, λ and μ are parameters representing the size of atoms. $f_R(r_{ij})$ is repulsive term, $f_A(r_{ij})$ is attractive term, and $f_c(r_{ij})$ is the function that changes the strength of the potential by changing the distance between particle i and j . b_{ij} represents many-body effect, as follows,

$$b_{ij} = \kappa_{ij} \left(1 + \beta_i^{n_{ij}} \zeta_{ij}^{n_{ij}} \right)^{\frac{1}{2n_i}} \quad (2.8)$$

where κ_{ij} is the parameter for the strength between different bonds: $\kappa_{ij} = 1$, $\kappa_{ij} = \kappa_{ji}$.

The quantity ζ_{ij} is represented as follows.

$$\zeta_{ij} = f_c(r_{ik}) g(\theta_{ijk}) \quad (2.9)$$

The function $f_c(r_{ik})$ changes the strength of the potential by changing the distance between particle i and k . The function $g(\theta_{ijk})$ is,

$$g(\theta_{ijk}) = 1 + \frac{c_i^2}{d_i^2} - \frac{c_i^2}{d_i^2 + (h_i - \cos \theta_{ijk})^2} \quad (2.10)$$

where θ_{ijk} is the angle of three particles ($\cos \theta_{ijk} = \mathbf{e}_{ij} \cdot \mathbf{e}_{ik}$). k is the center particle of the monomer where the particle i belongs. This function $g(\theta_{ijk})$ has a minimum at $h = \cos \theta_{ijk}$. The parameter d shows how sharp the

Figure 4. Example of four monomers with three cross-linkings. Black circles are center of four monomers A, B, C and D. White circles are reactive groups. The dashed lines are cross-linkings. We have $N_{elastic} = 3$ and $N_{max} = 16$ in this configuration.

dependence on angle is. c is the strength of the angular effect. All the parameters in the model potential are tabulated in Table I.

Choosing room temperature $T = 298K$, mass corresponding to the molecular weight 9617 ~ 11091, and arm length of 26.35 Å, the time step in our simulation corresponds to 66fs, and total times 0.42 μs . In the length unit of half the arm length of tetra-PEG, $l_0 = 13.18 \text{ Å}$, the box size is $L = 40$, with periodic boundary condition. The cut-off length of our potentials is $r_c = 5$. The number of macro-monomers is 300 (150 of α monomers and 150 of β monomers) for most of the following results except Fig. 12. The quantities in Section 3 were obtained by averaging over three samples.

Parameters are shown in Table I.

Table I. Potential parameters.

Δt	0.001	A_{ij}	1.4×10^3
ϵ_0	2.5	B_{ij}	3.5×10^2
m	2.0	λ_{ij}	3.5
r_0	2.0	μ_{ij}	2.2
K_{bond}	25.0	β_i	1.6×10^{-7}
K_{angle}	50.0	n_{ij}	7.3×10^{-1}
L	40.0	c_{ij}	3.8×10^4
ζ	20.0	d_{ij}	4.4
$k_B T$	6.0	h_{ij}	-1.0
S_{ij}	5.0	R_{ij}	2.0

3. RESULTS AND DISCUSSIONS

3.1 Gelation

In our definition of gel, we check two

Figure 5. Reaction ratio of tetra-PEG.

Figure 6. The time dependence of the number of monomers with different number of cross-linking. The number above the curve shows the number of cross-linking of each monomer.

conditions.

(1) We divide each axis, x , y , or z into 40 meshes, and check whether the projection of cluster to the axis occupies all meshes. If (1) is satisfied, we successively check the condition (2).

(2) We apply a mini-MD simulation with only the spring potential and attractive force to the center of the box. If the system shrinks to a compact structure, it is not gel. In Fig.3, we show a schematic presentation of percolation of the gel.

In Fig.3 (a), the condition (1) is not satisfied. Thus (a) is not gel. In Fig.3 (b), the condition (1) is satisfied, and we move to condition (2). After a mini-MD, the system shrinks to a compact structure. Thus (b) is not gel. In Fig.3 (c), condition (1) and (2) are satisfied. Thus, (c) is gel in our classification. This method, in practice of simulations, is very effective and practical because condition (1) is very quick, and we check condition (2) only for a limited number of cases. Once gelation is found at certain time step, the checking procedure is completed. Indeed, the gelation was found at about 19,000th step.

(a)

(b)

Figure 7. Newly formed cross-linkings measured every 10,000 steps. (1) inside the largest cluster (2) between other clusters (3) between the largest cluster and other clusters (4) inside other clusters. (b) is a vertical blowup of (a).

Figure 8. Classification of cross-linkings. (1) inside the largest cluster (2) between other clusters (3) between the largest cluster and other clusters (4) inside other clusters.

3.2 Reaction ratio

Reaction ratio is an important quantity, because it shows how much the gelation [8-10] has proceeded, and also because we can compare experiments and simulation results. In our simulation, we calculate the reaction ratio ρ as,

$$\rho = \frac{N_{el}}{N_{\max}}, \quad (3.1)$$

where N_{el} is the number of cross-linkings which

Figure 9. Distribution of number of loops at the end of the simulation. Horizontal axis specifies the loop length measured by the number of monomers.

Figure 10. Time dependence of the number of the loops of various length. The number in the figure shows the loop length. We searched loops up to twenty monomers, and found up to 14 monomers.

are attached to monomers with three or more cross-linkings and $N_{\max}$ is the number of all reactive groups.

In Fig. 4, of the four monomers A, B, C and D, only the monomer A has three or more cross-linkings. Thus, $N_{el} = 3$. The number of all the reactive groups is 4 times the number of monomers. Thus, $N_{\max} = 4 \times 4 = 16$. Therefore, we have $\rho = 3/16$ for Fig. 4. We use monomers with three or more cross-linkings, because they contribute to network elasticity, in accordance with the works of Miller et al. [8].

As shown in Fig. 5, reaction ratio at the gelation (19,000th step) is 17~21% in our simulation, which is comparable to the experimental value of 16-20%.

At the end of the simulation, the reaction ratio was more than 80%, which is much larger than the experimental value of 50-60%. This difference may be due to the following reasons. First, in our simulation, the random force effect inside the clusters may be larger than the experimental situation. Secondly, the bond angle may be closer to straight line in our model than the experiments.

3.3 Cross-linkings

(a)

(b)

Figure 11. Unreacted monomers at the end of simulation. Dark gray cone and light gray cone show reacted α and β particle, respectively. The sphere attached at the end of a rod is unreacted particle. In (a), all monomers, including unreacted and reacted monomers, are shown. In (b), only the unreacted monomers are shown.

We analyzed the number and types of cross-linkings before and after gelation. Figure 6 shows the time dependence of the number of monomers with different number of cross-linking. Compared with monomers with one, two or three cross-linkings, monomers with four cross-linkings have significantly slower rate of increase. This is because monomers with three cross-linkings cannot move freely, and it is difficult to form the fourth cross-linking. Since the gelation occurs at about 19,000th step, Fig. 6 reveals that gelation is caused by monomers with up to three cross-linkings.

The progression of gelation is associated with the growth of clusters of tetra-PEGs. We monitored the number of cross-linkings in the largest cluster and in the others, separately. As shown in Fig. 7, the crosslinkings are classified depending on the place where they newly appear. In Fig. 8, we show the number of newly formed cross-linkings for the classes as indicated in Fig.

Figure 12. Relation of unreacted particle and reacted particle. (a) $\alpha : \beta = 150 : 150$
(b) $\alpha : \beta = 100 : 100$

7. At the early stage, only the small clusters are formed. Later, larger clusters are formed by combining small clusters. Then, bigger clusters are formed by bonding of small clusters. After the gelation (19,000th step), most of the cross-linkings occur in the largest cluster, with cross-linking in the fourth reactive group (see Fig. 6).

3.4 Minimum loops

To investigate the mesh structure in the gel, we analyzed loops in the gel. Figure 9 shows the number of the loops at the end of the simulation. We have made a program-code which searches the loops that consist of up to twenty monomers. The loops that consist of fourteen or more monomer have never been detected. We found a maximum distribution at loop with eight monomers. Figure 10 shows the time dependence of the number of loops. After 200,000 steps, loops consisting of twelve or more monomers tend to decrease. After cross-linkings occur in the larger loop, it is divided into smaller loops. The loop consisting of eight monomers increases, when large loop is divided into smaller loops. Loops with eight monomers found at the end of simulation are due to the dividing of larger loops into smaller ones.

3.5 Unreacted monomers

Figure 11 shows the snapshots of the monomers with unreacted particles at the end of simulation. We found that the unreacted monomers remain, as the same types of monomers, are close together and cannot react with each other. In Fig.12, we

Figure 13. How to count the number of reacted and unreacted particles. From an unreacted particle at the center (square), we count the number of reacted particles (black circles) and unreacted particles (white circles) within radius r_c , which is the cutoff length of our potentials.

show the number of the unreacted and reacted particles around unreacted particles, with two different concentrations (a) and (b). Our method of counting the particle is shown in Fig.13. In this case we have six unreacted particles and five reacted particles. In Fig.12, we put a point at $x = 6, y = 5$.

At high concentration case (a), the unreacted particles are distributed widely, but it remains unreacted, so there is a possibility that the unreacted particles are obstructed by the surrounding particles. Moreover, the monomers with the unreacted particle are trapped by the clusters. The monomers with unreacted particles remain, because they are close to the same type of monomers (α and α , or β and β) or because they are trapped in a cluster of reacted monomers.

3.6 Mobility

To analyze the movement of monomers, the mobility of the center of gravity of monomer was examined. Figure 14 shows the time dependence of mobility of monomers with cross-linkings 0, 1, 2, 3, and 4. We measure the displacement of the center of mass of the monomers every 1,000 steps, where the gelation occurs at around 19,000 steps. Mobility for all cases shows sharp increase in the beginning before the gelation. This is because movement of the monomers is not restricted yet by other structures. The number of monomers with zero cross-linking decreases as the structure of gel develops. Mobility of monomers with one cross-linking is seen with large fluctuation. The mobility of monomers with three or more cross-linkings is stable after the gelation, with keeping mobility around unity (l_0). These behaviors are considered to come from vibrations of tetra-PEGs in the cluster. In the dilute limit of

Figure 14. Mobility of the center of mass of monomers with number of cross-linkings (a) 0, (b) 1, (c) 2, (d) 3, (e) 4. The mobility is measured by the displacement every 1,000 time steps.

particles, the mobility may decrease as the number of cross-linking increases. However, our results show that mobility is about the same for two, three or four cross-linkings, which may be due to the obstruction of movements by surrounding monomers.

In the experiments, it is possible to make the

gel from the monomers with trifunction group. It will be interesting to compare the case of trifunction group with the case of tetrafunction group, and to determine which gives more homogenous mesh. The fourth unreacted group may be considered impurity in the mesh. On the other hand, the fourth cross-linking may give more homogeneous structure.

Further investigation is necessary to explore the case of higher concentration with more refined model and to compare the simulation results with experimental data.

4. SUMMARY

We have studied reaction ratio, dynamics and structure of tetra-PEG gel by using a coarse grained model. We found that gelation is caused by monomers with up to three cross-linkings, and found that the large loop is divided into small loops by fourth cross-linking. We analyzed the mesh structure, and found that loops with eight monomers are most abundant, because division from a large loop to small loops occurs in the largest cluster. Such division may prompt the uniformity in the gel, confirming the property of the strength gel.

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