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Dissipative Particle Dynamics Simulation Parameters and Interactions of A Hydrogel

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Abstract: In this work, we report a parameterization procedure to compute the parameters of a hydrogel consisting of a hydrophilic polymer and a cross-linker. The system is parameterized so that coarse-grained dissipative particle dynamics (DPD) simulations can be performed. Proper computation of the simulation parameters is crucial in order to represent the inherent chemical nature of the hydrogel and to model the correct structure. The polymer is parameterized by considering different volumes for coarse-grained beads. Moreover, the hydrogen bond interactions should be represented and properly defined in the simulations. To that purpose, we use a recently introduced parameterization procedure that incorporates the attraction as a result of the hydrogen bond interactions between relevant beads. This paper serves as an example of how the realistic simulation parameters of a hydrophilic polymer can be straightforwardly computed by leading to a proper determination of the structure and properties. The computational background, the procedures and the results of the computation are reported and discussed in this paper.

Keywords: Dissipative Particle Dynamics method, coarse-grained simulations, polymers.

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INTRODUCTION

Hydrophilic polymers are widely used in biomedical area as hydrophilicity is desired for various properties, such as lubricity, biocompatibility, wear comfort, and anti-fouling, which would reduce the risk of infection or different clinical problems (1-5). A thorough understanding of the proper structure and dynamics of such materials will pave the way of designing new materials with distinctive features for special purposes. In this work, we study the interactions and structural properties of a hydrogel that is formed by the reaction of a hydrophilic polymer and a cross-linker. Being a hydrogel, the material interacts with water during functioning. The material that we investigate in this work is a cross-linked PEG. PEG was previously studied by performing extensive molecular dynamics simulations for example, to model drug encapsulation (6), to stabilize insulin (7) or to model drug release (8). Moreover, there are also coarse-grained simulation approaches to obtain its structure by Lee and co-workers (9), by Prasitnok and co-workers to study its structure in wet environment (10), and in more complex environments such as attached to lipids (11) or dendrimers (12).

In this work, molecular and mesoscopic scale interactions are studied since intrinsic time and length scales that are valid for the creation of hydrogel structure are at nano- and micro-second levels. The simulation method is referred to as Dissipative Particle Dynamics (DPD). DPD is a coarse-grained simulation method where the different number of atoms, that represent different functional groups, are combined to form the so-called *beads*. By this coarse-graining procedure, the polymer can be equilibrated within a reasonable amount of time. DPD is often applied to study the behavior of complex fluids (13), polymers (14-18), surfactants (19), colloids (20) *etc*. The original DPD parameterization requires beads having similar volumes. This is a serious limitation of the method upon application to real molecular systems. In experimental systems, polymers can have beads with different molar volumes. In this work, we use an alternative parameterization method where a pure-liquid density-dependent parameterization is used (17). This procedure results in beads having different volumes. Especially for cross-linked systems, correct representation of bead volumes is extremely important since the resulting structure cannot be corrected after cross-linking. Besides variable bead volumes of polymeric systems, a particular attention should be paid to modeling the hydrogen bond interactions which are present in hydrophilic systems. For that purpose, we use a recently developed parameterization where the hydrogen bond attraction is explicitly modeled in DPD simulations (21). The parameterization procedure for parameterizing the DPD potential involves addition of a Morse potential term to the DPD potential. A similar procedure is performed to study the α −helical and β-sheet structures of proteins (22). In this work, the parameters defining the Morse potential are set arbitrarily in order to create the target protein structure with no scaling by physical units, therefore without taking proper chemistry of beads into consideration. However in our work, we attempted to compute the hydrogen bonding parameters by considering the exact chemical nature of molecules by combining the results of atomistic simulations with experimental Flory-Huggins parameters. The work in reference (21) demonstrates that the experimental negative volume excess of hydrogen bonding for low molecular weight alcohol and water mixtures can be predicted from coarse-grained simulations.

In this work, we aim to present a parameterization for DPD simulations, where polymeric materials interacting with water can be modeled. The procedure presented herein, extends the applicability of DPD to a wider range of polymers in contact with wet environments. The contents of the paper can be outlined as follows: Initially, the details of the DPD method are discussed. Second, the parameterization procedure and the results of the calculations are given. Finally, the values are discussed to demonstrate a qualitative structural analysis of the hydrogel. This paper targets to introduce a coarse-grained parameterization procedure that can be applied to any hydrophilic material, and to discuss the interactions of the polymer resulting in the equilibrium structure.

MATERIALS AND METHODS

Dissipative Particle Dynamics Simulation Method

The total force that applies to a particular bead is the addition of conservative, random, and dissipative forces. The conservative force characterizes the equilibrium structure, while the random and dissipative forces operate collectively and regulate the temperature. The non-bonded potential of DPD is given as:

$$V_{\mathrm{DPD},ij}(r) = \begin{cases} \dfrac{a_{ij}}{2}\left(1 - \dfrac{r}{r_{\mathrm{DPD}}}\right)^2 & r < r_{\mathrm{DPD}} \\ 0 & r \geq r_{\mathrm{DPD}} \end{cases} \tag{Eq. 1}$$

where r_{DPD} is the cut-off value, and a_{ij} is the DPD interaction strength between beads *i* and *j* in dimensions $k_{\mathrm{B}}T$.

The previously proposed alternative parameterization of DPD dictates the variable volumes of beads as a function of their pure-liquid densities by the relation: (17)

$$a_{ij} = \hat{a}_{ij} + \frac{p}{0.0454(a_{ii}\rho_{i,\mathrm{pure}} + a_{jj}\rho_{j,\mathrm{pure}})}\chi_{ij}k_{\mathrm{B}}T, \qquad \hat{a}_{ij} = \sqrt{a_{ii}a_{jj}}$$

$$\text{with } a_{ii} = \frac{p - \rho_{i,\mathrm{pure}}k_{\mathrm{B}}T}{\alpha\rho_{i,\mathrm{pure}}^2 r_{\mathrm{DPD}}^3} \tag{Eq. 2}$$

In Eq. 2, a_{ii} and a_{jj} are like-like interactions of beads i and j, $\hat{a}_{ij}$ is the neutral interaction parameter, and ρ_i represents the dimensionless number densities of the pure components. The parameter α is taken here as constant and equals to 0.101 for number densities higher than 3, as demonstrated by Groot and Warren's original work on DPD parameterization (23).

There is a linear relation in between Δa_{ij} and the experimental quantities following $\Delta a_{ij} = \mathrm{C} \times \chi_{ij} k_\mathrm{B} T$. Here, χ_{ij} is the Flory-Huggins parameter (24) and Δa_{ij} quantifies the excess repulsion. *C* is a constant defining the slope of the linear relationship between Flory-Huggins parameter and the DPD parameter, and is equal to 0.286 for a number density of 3. The pressure *p* is set to represent an overall compressibility value of the mixture and taken as 40 $k_\mathrm{B}T/r_\mathrm{DPD}^3$. Flory-Huggins χ_{ij} parameter is related to the solubility parameters via the relation:

$$\chi_{ij} = \frac{V_\mathrm{m}}{RT}(\delta_i - \delta_j)^2 \qquad \text{(Eq. 3)}$$

where δ's are the solubility parameters and V_m is the molecular volume of a bead. The relationship between the χ_{ij} parameter and the excess repulsion is reported in Groot and Warren's original DPD work (23).

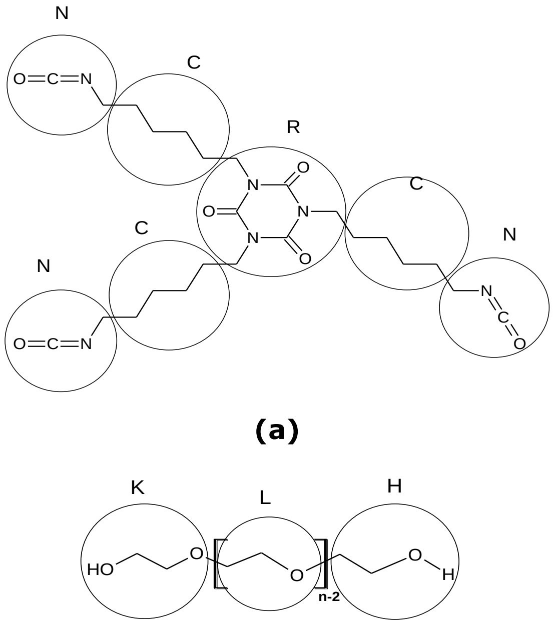
The implementation of hydrogen bonds to DPD method is performed by adding a Morse potential term to the non-bonded DPD potential.

$$V_\mathrm{Morse} = D_0\left[\mathrm{e}^{-2\sigma(r-r_0)} - 2\mathrm{e}^{-\sigma(r-r_0)}\right], \quad r < r_\mathrm{DPD} \qquad \text{(Eq. 4)}$$

In this equation, D_0 represents the strength of the attraction, σ quantifies the curvature, and r_0 is the equilibrium distance (21). We select a value of $2/r_\mathrm{DPD}$ for σ. In Eq. 4, the contribution of hydrogen bonds are not counted for inter-bead distances larger than 1 r_DPD.

Hydrophilic polymer structure and the coarse-graining

The hydrogel consists of a combination of a trimerized hexamethylene diisocyanate (tHDI) cross-linker and a polyethylene glycol (PEG) spacer with a molecular mass of 2000 g/mol. The mixture is at the stoichiometric ratio of 2:3. As previously mentioned, the coarse-graining is performed by partitioning the chemical structure into chemically meaningful units as depicted in Figure 1. In accordance with the stoichiometry, the total number of beads in each chain are set to 1000 for tHDI and 1500 for PEG chains.



(a)

(b)

Figure 1: Schematic representation of the coarse-grained beads of (a) tHDI and (b) PEG.

RESULTS AND DISCUSSION

Initially, the Flory-Huggins interaction parameters which quantify the mixing behavior of the molecules (24) are determined. These parameters are obtained from Eq. 3 by identifying the van Krevelen solubility parameters from group contribution methods (25). Here, Molecular Modeling Pro Software (26) is used. In Table 1, we report the computed χ_{ij} parameters.

χ_{ij}	**N (24.58)**	**C (13.84)**	**R (29.56)**	**L, H (25.09)**	**K (31.86)**	**N′ (22.01)**	**W (47.00)**
N	0.00	2.84	0.61	0.01	1.30	0.16	12.36
C	2.84	0.00	6.08	3.12	7.99	1.64	27.04
R	0.61	6.08	0.00	0.49	0.13	1.40	7.48
L, H	0.01	3.12	0.49	0.00	1.12	0.23	11.79
K	1.30	7.99	0.13	1.12	0.00	2.39	5.63
N′	0.16	1.64	1.40	0.23	2.39	0.00	15.36
W	12.36	27.04	7.48	11.79	5.63	15.36	0.00

Table 1: Computed Flory-Huggins parameters of the coarse-grained beads. N′ bead represents the reacted N bead upon cross-linking. Values in parentheses indicate the solubility parameters in dimension $(J/cm^3)^{0.5}$. W bead represents single water molecule.

A DPD fluid phase separates out if the value of χ is above 2 (23). Therefore, the χ values in Table 1 higher than 2 indicate a phase-separation. The largest difference of χ value is in between C and K beads, whereas the smallest difference is in between N and L (or H). We named L and H beads differently, although they have the same chemical structures.

The reason is to differentiate the head group and the repeating units of PEG. The repelling interactions of C and K can be explained monitoring the internal chemical structures of C and K beads. The C bead is nothing but a butane molecule which is nonpolar in principle. On the other hand, K bead is a polar molecule that can make hydrogen bonds with particular molecules. According to the values in Table 1, the bead pair that like each other the most is the N and L pair. They are similar in size, both are polar and have high chances to form hydrogen bonds with each other.

If we examine water and polymer bead interactions, it is seen that all beads have a tendency to repel each other. The smallest χ parameter values are observed in between K and W, and R and W beads among the others. The solubility parameters corresponding to water and polymer beads differ to a large extent. The difference of solubilities and resulting high values of χ parameters would lead to a large separation of polymer and water beads in the simulations. The exact repulsive nature of the interactions can be analyzed and discussed in the form of self and pairwise interactions of DPD. To that purpose, Eq. 2 and Table 1 are combined to compute the corresponding a_{ij} parameters. The calculated values are given in Table 2.

a_{ij}	**N (0.0113)**	**C (0.0062)**	**R (0.0038)**	**L, H (0.0103)**	**K (0.0112)**	**N′ (0.0094)**	**W (0.0033)**
N	**31.26**	65.78	96.80	34.29	36.68	38.10	89.36
C	65.78	**106.39**	186.28	71.82	80.58	73.54	120.79
R	96.80	186.28	**292.22**	105.71	96.01	117.28	47.10
L, H	34.29	71.82	105.71	**37.55**	38.73	41.93	81.08
K	36.68	80.58	96.01	38.73	**31.37**	46.46	45.89
N′	38.10	73.54	117.28	41.93	46.46	**44.96**	96.72
W	89.36	120.79	47.10	81.08	45.89	96.72	**2.90**

Table 2: DPD interaction parameters a_{ij} of the coarse-grained beads. N′ bead represents the reacted N bead upon cross-linking. The values in parentheses represent the dimensionless number densities of beads ρ_i obtained by $\rho_i = \rho_{i,\mathrm{liquid}} / M_{\mathrm{W},i}$. W bead represents the single water molecule.

We discuss the relative repulsions of beads by considering the difference in the values of pairwise and like-like interactions, which is critical since like-like interactions are different for each bead correlated with the bead volume. For example, the bead having the largest volume is the R bead and the one with the smallest volume is the N bead. Consequently, these beads have the highest and the lowest like-like interaction values, respectively. In line with the Flory-Huggins parameters in Table 1, the most repulsive interaction is in between C and K beads, although the numerical value of corresponding a_{ij} is smaller than most of the values in Table 2, whereas N and L bead pair has the lowest repulsion strength. This means in a simulation, that C and K will be separated, on the other hand, the L bead would like to stay even closer to N bead rather than itself due to a lower a_{ij} value than its like-like interaction value.

The like-like interaction value of water is the lowest among the polymer beads due to its smallest size. However, the pairwise interactions between the water bead and the other type of beads are larger. This indicates a preference of water to stay close to the same type of beads rather than moving near polymer beads. The highest repulsion of water is with the C bead since it is purely composed of carbon atoms. The least repulsion strength is observed in between the R and W beads. This value is even smaller than the like-like interaction of the R bead. The hydrogen bond contribution to solubilities has an influence favoring mixing. Obviously, if these values are used in a simulation, the polymer and water would be phase-separated, with the exception of hydrophilic polymers. The analysis of the DPD parameters solely identifies the importance of contribution of hydrogen bonds to the DPD method.

In this section, we use a parameterization that was recently proposed to add hydrogen bond attraction to the purely repulsive DPD potential (21). The added term will be in the form of a Morse potential. A multi-scale procedure is used to compute the Morse potential parameters which take atomistic molecular dynamics simulations as the basis. In this procedure, the hydrogen bond energy is computed for different hydrogen bonding pairs from the potential energy differences of the mixture and the pure components. The second parameter of the Morse potential, namely the equilibrium hydrogen bond distance, is computed from the radial distribution functions (RDF). The exact form of equations and procedure is given in detail in reference (21).

Upon coarse-graining of the PEG, the repeating unit is solely an ethanol molecule. In this work, we adapted the Morse potential values for the system of interest from the reference study. The repeating unit constitutes a large portion of the mixture due to the rule of stoichiometry. Therefore, the structure of polymer is dominantly characterized by the interactions of this bead. For the rest of the beads, the Morse potential parameters are computed by taking the strength of ethanol-water hydrogen bond interaction as reference and scaling its value with the number of possible hydrogen bonds. For example, the strength of hydrogen bond interaction of R and water beads is computed by multiplying ethanol-water hydrogen bond interaction strength by six, since R bead can make six hydrogen bond interactions with water. In this way, we get a reasonable approximation to the overall hydrogen bond interactions, and at the same time differentiate the hydrogen bond strengths of different materials favoring higher attraction if the number of hydrogen bonds is higher. The equilibrium hydrogen bond distance is taken as the same value for ethanol-water interaction without performing any scaling since the hydrogen bond equilibrium distance does not change significantly according to the type of material as observed in reference (21).

The polymer is in the form of a hydrogel. Therefore, if immersed in, the material can take up a significant amount of water. The hydrogen bond strength and hydrogen bond equilibrium distance values change as a function of water content in the total mixture. The corresponding values are computed by a linear interpolation using the linear fit parameters reported previously (21). As examples, we demonstrate in Table 3, the Morse potential parameters for two mixtures with different water contents.

As shown in Table 3, the values differ following the variation in water content in the total mixtures. This is a result of the linear increase of the hydrogen bond strength with respect to the decrease in the amount of water in the mixture (21). The strongest hydrogen bond attraction with water is observed for the center bead of tHDI molecule, the R bead, whereas the weakest hydrogen bond attraction with water is formed in presence of the K bead of PEG chain. The hydrogen bond strengths tabulated in Table 3 are a function of the number of possible hydrogen bond connections and the overall molar fraction as dictated by the linear relationship reported in reference (21). The equilibrium hydrogen bond distance values also do change according to the change of the physical length-scale of DPD r_{DPD}.

Bead type	**25%**			**75%**		
	x_i	D_0 [k_BT]	r_0 [r_{DPD}]	x_i	D_0 [k_BT]	r_0 [r_{DPD}]
N	0.03	12.95	0.53	0.01	12.53	0.51
R	0.01	37.58	0.51	0.00	37.16	0.50
L, H	0.66	13.07	0.77	0.22	8.46	0.69
K	0.02	12.63	0.51	0.01	12.42	0.50
N′	0.03	12.95	0.53	0.01	12.53	0.51

Table 3: Morse potential parameters for 25% and 75% water content in the total mixture. x_i represents the molar fraction of individual beads.

CONCLUSIONS

This paper targets to construct a DPD parameterization scheme where a hydrogel is modeled in order to perform coarse-grained simulations. The beads that constitute the hydrogel are parameterized in such a way that their volumes are set to be different and dictated by their pure-liquid volumes. Moreover, we apply a recently proposed parameterization method where a Morse potential mimics the inter-molecular attraction as a result of the hydrogen bonds. The Morse potential parameters, namely hydrogen bond strengths and equilibrium hydrogen bond distances, are computed by taking the internal chemistry into account. Besides providing the coarse-grained parameterization details, we discuss the inherent interactions that are present and make a qualitative analysis of the structure as well. The validation of the parameterization procedure is saved as a separate future work. The coarse-grained parameterization procedure of the specific polymer reported in this work can be used as a general tool that can be applied to any similar material. Nevertheless, the procedure reported herein would drag attention of the researchers not only from computational but experimental communities.

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