

# A Surface Site Interaction Point Method for Dissipative Particle Dynamics Parametrization: Application to Alkyl Ethoxylate Surfactant Self-Assembly.

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**ABSTRACT:** Dissipative particle dynamics (DPD) is a coarse-grained approach to the simulation of large supramolecular systems, but one limitation has been that the parameters required to describe the non-covalent interactions between beads are not readily accessible. A first principles computational method has been developed so that bead interaction parameters can be calculated directly from *ab initio* gas phase molecular electrostatic potential surfaces of the molecular fragments that represent the beads. A footprinting algorithm converts the molecular electrostatic potential surfaces into a discrete set of surface site interaction points (SSIPs), and these SSIPs are used in the SSIMPLE (surface site interaction model for the properties of liquids at equilibrium) algorithm to calculate the free energies of transfer of one bead into a solution of any other bead. The bead transfer free energies are then converted into the required DPD interaction parameters for all pairwise combinations of different beads. The reliability of the parameters was demonstrated using DPD simulations of a range of alkyl ethoxylate surfactants. The simulations reproduce the experimentally determined values of the critical micelle concentration and mean aggregation number well for all 22 surfactants studied.

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## INTRODUCTION

The formation of supramolecular structures such as micelles, vesicles and bilayer membranes is a fundamentally important process in biology and in industry, with many applications in health and personal care products.<sup>1</sup> The self-assembly of surfactants is a complicated process, and despite the development of simple tools that can be used to predict some aspects of surfactant behavior based on chemical structure (*e.g.* the critical packing parameter<sup>2</sup> and the hydrophilic lipophilic balance (HLB)<sup>3</sup>), the development of new surfactant systems still relies on experimental screening. The key parameters are the critical micelle concentration (CMC), which is the concentration at which surfactants start to aggregate into supramolecular structures (micelles), and the mean aggregation number ( $N_{\text{agg}}$ ), which is the average number of surfactants in a micelle. Common techniques used to measure the CMC are surface tension,<sup>4</sup> dynamic light scattering (DLS),<sup>5</sup> fluorescence,<sup>6</sup> UV-Vis<sup>7</sup> and NMR<sup>8</sup> spectroscopy, and in the case of charged species, conductometry<sup>9</sup> and capillary electrophoresis.<sup>10</sup> Methods for determining the  $N_{\text{agg}}$  include DLS,<sup>11</sup> small angle neutron diffraction,<sup>12</sup> and time-resolved fluorescence quenching.<sup>13</sup>

Many factors affect these measurements: for example, temperature, the presence of electrolytes, and organic impurities in the solution.<sup>14-15</sup> The method of analysis also plays a role, because different methods are sensitive to different aspects of the self-assembled supramolecular structure.<sup>16</sup> As a result, experimental screening of new surfac-

tant formulations is time-consuming and expensive, and *in silico* prediction of surfactant self-assembly processes would be an attractive alternative. One computational approach is all-atom molecular dynamics (MD), but due to the long equilibration times and the large numbers of molecules required, coarse graining (CG) approaches are the method of choice.<sup>17</sup> Coarse-graining combines several atoms or molecules into single CG beads, reducing the number of force centres and the associated computational cost.

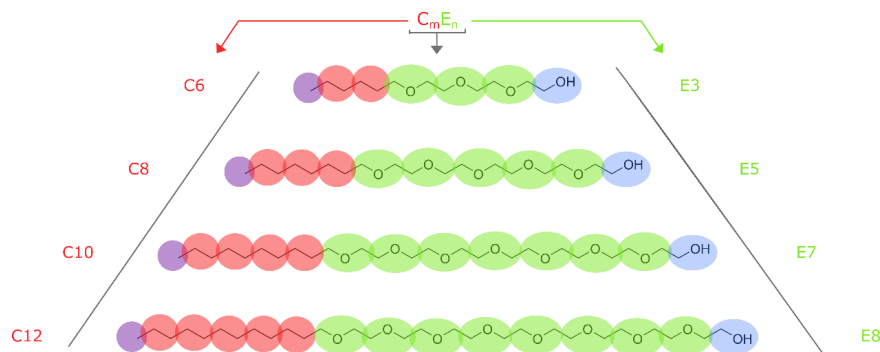
Various CG methods have been used for the prediction of surfactant behaviour in solution, including Monte Carlo (MC)<sup>18</sup> and lattice Boltzmann methods.<sup>19</sup> Although recent progress in coarse grained molecular dynamics (CG-MD), using force-fields such as MARTINI shows promise,<sup>20-22</sup> the size of the simulated systems using Lennard-Jones potentials with hard-core repulsions is still limited in length and timescale. One of the possibilities for further increasing the computational efficiency is the use of methods that consider only soft-core interactions, such as dissipative particle dynamics (DPD). Originally developed by Hoogerbrugge and Koelman<sup>23</sup> and extended by Español and Warren,<sup>24</sup> DPD uses soft-core beads, which move according to Newton's equations of motion.

The total force acting on a DPD bead is the sum of a conservative force, a drag force, and a random force. The drag and random forces are used solely for thermostating (NVT ensemble).<sup>24</sup> The conservative force derives from a short-range soft pair potential of the form

$$U_{ij} = \frac{1}{2} a_{ij} \left( 1 - \frac{r_{ij}}{R_{ij}} \right)^2 \quad \text{for } r_{ij} < R_{ij}, \quad \text{Eq. 1}$$

where  $a_{ij}$  is the repulsion amplitude describing the interaction between bead  $i$  and bead  $j$ ,  $r_{ij}$  is the distance between the two beads, and  $R_{ij}$  is the cut-off distance beyond which there is no interaction between the beads.

Since the conservative force accounts for the difference in non-covalent interactions between different beads, determination of the parameters in Equation 1 is critical for accurately reproducing the relationship between chemical structure and surfactant behavior.



**Figure 1.** Coarse grained representation of alkyl ethoxylate ( $C_mE_n$ ) surfactants. The hydrocarbon chain is represented by a bead for the  $CH_3$  terminal group (purple) and beads for ethylene groups (red). The glycol chain is represented by a bead for the terminal alcohol moiety (blue) and beads for the  $CH_2OCH_2$  groups (green).

Much effort has gone into the development of systematic parametrization methods to obtain the DPD repulsion amplitudes  $a_{ij}$ . An early approach by Groot and Warren links  $a_{ij}$  with Flory-Huggins  $\chi$ -parameters.<sup>25</sup> This correlation has been used to obtain  $a_{ij}$  from experimental solubility data,<sup>26</sup> Hildebrand cohesive energy density parameters,<sup>27-28</sup> and infinite dilution activity coefficients.<sup>29</sup> Alternatively,  $a_{ij}$  can be obtained by using experimental data on the mutual solubility of small molecules. For example, using the CG approach for the alkyl ethoxylate surfactants shown in Figure 1, the interaction between the terminal alcohol bead and a bead in the ethylene glycol chain could be obtained using the mutual solubilities of methanol and methoxymethane. Computational approaches have also been investigated as an alternative to empirical parameterisation.<sup>30-32</sup> A combination of MC and MD simulations was used to derive relationships between Flory-Huggins  $\chi$ -parameters and  $a_{ij}$  values for interactions between different sized beads.<sup>33</sup> COSMO-RS was used to calculate infinity dilution activity coefficients and 1-octanol/water partition coefficients in order to obtain DPD repulsion parameters.<sup>34-36</sup>

However, estimation of repulsion amplitudes based on experimental or calculated molecular properties has some limitations. Since DPD beads typically represent a fragment of a molecule, in reality a portion of the molecular surface is buried by the overlap between covalently connected beads; this area should not be included when computing the bead interactions. Computational approaches provide an opportunity to remove the regions of bead overlap from a molecular surface. Saathoff used COSMO-SAC to delete parts of the molecular surface in the calculation of solvation free energies.<sup>31</sup> An alternative approach to avoid this problem was adopted by Anderson *et al.* who used DPD simulations of the partition coefficients of complete molecules to optimize the set of  $a_{ij}$  values, fitting to experimentally data.<sup>37</sup>

Here, we propose a new approach to the calculation of DPD bead repulsion amplitudes  $a_{ij}$  using surface site interaction points (SSIPs).<sup>38</sup> We develop the method in the context of CG models of

alkyl ethoxylate surfactants shown in Figure 1. In this approach, different beads are used to represent chemical sub-groups containing between one and three heavy atoms as in Anderson *et al.* This provides flexibility and allows straightforward extension to more complicated systems. We show by simulation that the  $a_{ij}$  values thus obtained accurately reproduce the experimental CMC and  $N_{agg}$  values for this class of non-ionic surfactants.

## APPROACH

Surface site interaction points (SSIPs) provide a quantitative description of all intermolecular interactions that a molecule can make with its environment. Molecules are represented as discrete sets of SSIPs of surface area  $10 \text{ \AA}^2$  and volume  $5 \text{ \AA}^3$  as illustrated in Figure 2. The number and properties of the SSIPs required to represent a specific molecule are calculated using the *ab initio* molecular electrostatic potential surface and a footprinting algorithm.<sup>39</sup> SSIPs can be used in the surface site interaction model for the properties of liquids at equilibrium (SSIMPLE) algorithm described in reference 38 to calculate solvation free energies and partition coefficients, which as we have outlined above can be used for estimating the  $a_{ij}$  parameters required for DPD.

In SSIMPLE, the solvent and solute molecules are each described as an ensemble of SSIPs. The equilibrium constant for the pairwise interaction of any two SSIPs is given by

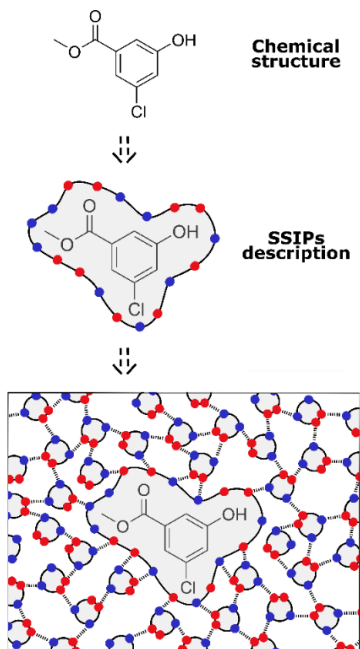
$$K_{ij} = \frac{1}{2} e^{-(\epsilon_i \epsilon_j + E_{vdw})/RT} \quad \text{Eq. 2}$$

where  $\epsilon_i$  and  $\epsilon_j$  describe the interaction properties of two SSIPs, and  $E_{vdw}$  is a constant that was estimated to be  $-5.6 \text{ kJ mol}^{-1}$  based on experimental data on the enthalpy change for the vapour-liquid equilibria of non-polar liquids as described in references 38 and 40.

The values of  $K_{ij}$  can be used to determine the speciation of all possible SSIP contacts in a liquid phase. For a solute SSIP  $x$  dissolved in a solvent S1, solving the set of simultaneous equations allows calculation of

$$K_{S1}(x) = [x_{\text{bound}}] / [x_{\text{free}}] \quad \text{Eq. 3}$$

where  $[x_{\text{bound}}]$  is the concentration of SSIP  $x$  that is bound to a solvent SSIP, and  $[x_{\text{free}}]$  is the concentration of SSIP  $x$  that is free. This represents the overall equilibrium constant for the interaction of SSIP  $x$  with the solvent. The SSIP description of non-covalent interactions was parameterized using equilibrium constants for H-bonded complexes, which were measured at room temperature, and the approach has not yet been generalized to different temperatures, so this paper will focus on the room temperature behavior of surfactants.



**Figure 2.** Calculation of the free energy of solvation based on pairwise contacts between SSIPs that describe non-covalent interactions between solute and solvent.<sup>38</sup>

Equating the concentrations of free SSIPs in two different phases allows calculation of the change in free energy ( $\Delta G_{12}$ ) for moving an SSIP from solvent 1 to solvent 2, according to

$$\Delta G_{12}(x) = RT \ln \left( \frac{1+K_{S1}(x)}{1+K_{S2}(x)} \right) + RT \ln \left( \frac{\theta_2 (\sqrt{1+8\theta_1}-1)}{\theta_1 (\sqrt{1+8\theta_2}-1)} \right) \quad \text{Eq. 4}$$

where  $\theta_1$  and  $\theta_2$  are the fractional occupancies of the two phases, equal to the total SSIP concentration relative to the maximum possible SSIP concentration (300 M), R is the gas constant and  $T$  is the absolute temperature.

Equation 4 represents  $\Delta G_{12}$  as the sum of a binding free energy, which accounts for the interactions the SSIP makes with the solvent SSIPs (first term), and a confinement free energy (second term). The confinement energy term is obtained by using an equilibrium constant of unity for all pairwise interactions in a phase and corrects for the difference in the probability of interaction associated with constraining the SSIPs to phases with different overall SSIP concentrations. For a solute molecule which is represented by multiple SSIPs, the free energy of transfer between two phases is calculated by summing the values of  $\Delta G_{12}$  over all SSIPs. Similarly, it is possible

to represent a DPD bead as a set of SSIPs and to calculate the free energies of transfer of beads between different liquid phases as the sum of the free energies of transfer of the individual SSIPs that represent the bead. These free energies of transfer are then used to obtain DPD repulsion amplitudes  $a_{ij}$  as follows.

First, the Flory-Huggins  $\chi$  parameter is calculated from the bead transfer free energy using Equation 5, which corrects for differences in the volumes of different beads.<sup>41</sup>

$$\chi = \frac{1}{2} \frac{v_r}{RT} \left( \frac{\Delta G_{12}}{v_1} + \frac{\Delta G_{21}}{v_2} \right). \quad \text{Eq. 5}$$

where  $v_r$ ,  $v_1$  and  $v_2$  are the van der Waals volumes calculated using the 0.002 electron/bohr<sup>3</sup> electron density isosurface for two molecules of water, and the fragments that represent beads 1 and 2 respectively, and  $\Delta G_{12}$  is the calculated change in free energy of transfer of one mole of bead 1 from a pure liquid composed of bead 1 to a dilute solution in a liquid composed of bead 2.

Second, the linear correlation proposed by Groot and Warren is used to obtain the actual DPD repulsion parameters using Equations 6 and 7.<sup>25</sup>

$$\Delta a_{ij} = \frac{\chi}{c_p}, \quad \text{Eq. 6}$$

where  $c_p = 0.291$  is a constant appropriate to the overall DPD bead density  $\rho r_c^3 = 3$  used in this work.<sup>25</sup>

$$a_{ij} = \frac{a_{ii} + a_{jj}}{2} + \Delta a_{ij}, \quad \text{Eq. 7}$$

where  $a_{ii}$  and  $a_{jj}$  are the self-interaction parameter for beads  $i$  and  $j$ .

One of the limitations of this method is that the interaction between beads of the same type,  $a_{ii}$ , cannot be calculated. One approach is to use the same self-interaction parameter for all beads, and the water  $a_{ii}$  parameter derived from compressibility data is commonly used (25 k<sub>B</sub>T).<sup>27</sup> However, this approximation assumes that all beads have the same volume,<sup>25</sup> so we use self-interaction parameters reported by Anderson *et al.*, which were tuned to match the experimental densities of selected molecular liquids.<sup>37</sup>

## RESULTS AND DISCUSSION

### DPD PARAMETERS

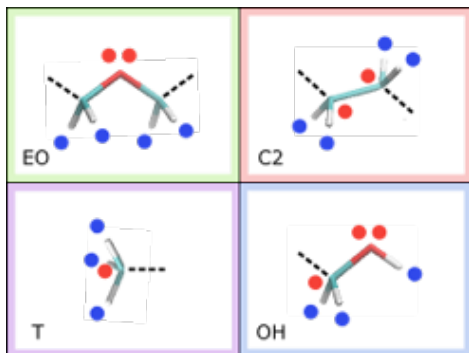
The SSIP description of the four beads required for DPD simulations of the surfactants in Figure 1 is shown in Figure 3. SSIPs were calculated using methoxymethane for EO, ethane for C2, methane for T and ethanol for OH. To convert these molecular descriptions to bead descriptions, the SSIPs associated with the hydrogen atoms located at the points of covalent connectivity between beads were removed, *i.e.* the points indicated by dotted lines in Figure 3. The SSIP description of water has been reported previously,<sup>43</sup> and the SSIP values used for all of the beads are summarised in Table 1. These values were used in SSIMPLE to calculate free energies of transfer for all pairwise combinations of beads (Table 1). A concentration of 1 mM was used for the solute beads to make sure that there are no solute-solute interactions, so the results are equivalent to the infinite dilution values required for Equation 5. The concentrations of the solvent beads were estimated based on structurally related liquids: the concentration of methanol was used as the bead concentration for a liquid composed of OH beads, half of the concentration of dimethoxyethane was used as the bead concentration for a liquid

composed of EO beads, one quarter of the concentration of *n*-octane was used as the bead concentration for a liquid composed of C2

beads, and one eighth of the concentration of *n*-octane was used as the bead concentration for a liquid composed of T beads.

**Table 1** SSIP representation of DPD beads and calculated free energies of transfer ( $\Delta G_{12}$  in  $\text{kJ mol}^{-1}$ ).

Bead	$v_i (\text{\AA}^3)$	SSIP $\epsilon_i$	$\Delta G_{\text{T}}$	$\Delta G_{\text{C2}}$	$\Delta G_{\text{EO}}$	$\Delta G_{\text{OH}}$	$\Delta G_{\text{W}}$
T	25.9	0.4, 0.4, 0.4, -0.3	0.00	0.40	0.00	2.40	18.38
C2	38.9	0.4, 0.4, 0.4, 0.4, -0.3, -0.3	-0.60	0.00	0.10	2.30	17.89
EO	48.7	0.4, 0.4, 0.4, 0.4, -5.3, -5.3	-1.14	-0.04	0.00	-1.52	-6.17
OH	34.7	2.7, 0.4, 0.4, -5.3, -5.3, -0.3	14.58	15.95	1.27	0.00	-3.16
W	42.0	2.8, 2.8, -4.5, -4.5	25.33	26.01	-0.71	0.50	0.00



**Figure 3.** SSIP representations of the DPD beads used in this work. Positive and negative SSIPs are shown as red and blue dots respectively. The dotted lines indicate the point of covalent attachment to adjacent beads.

**Table 2:** DPD parameters for all pairwise bead interactions.

Bead $j$	Bead $i$	$a_{ii}^{36}$	$a_{ij}$	$\Delta a_{ij}$	$R_{ij}^{36}$
C2	C2	22.0	/	/	1.074
EO	EO	25.5	/	/	1.116
OH	OH	14.0	/	/	0.980
W	W	25.0	/	/	1.000
T	T	24.0	/	/	0.955
C2	EO	/	23.8	0.03	1.095
C2	OH	/	27.1	9.13	1.027
C2	W	/	45.5	21.95	1.037
EO	OH	/	19.6	-0.13	1.048
EO	W	/	21.8	-3.44	1.058
OH	W	/	18.2	-1.33	0.990
T	W	/	46.2	21.85	0.978
T	OH	/	27.5	8.49	0.968
T	C2	/	22.9	-0.08	1.015
T	EO	/	24.2	-1.05	1.036

The transfer free energies in Table 1 were used in Equations 5-7 to obtain the repulsion parameters listed in Table 2. For beads of different size, a volume correction is used in Equation 5. The van der

Waals volume of the terminal beads T and OH was calculated by using half the calculated volume of ethane and 1,2-ethandiol, respectively. For the inner beads C2 and EO, the van der Waals volumes were obtained by calculating the volumes of homologous series of alkanes or ethylene glycols and taking the slope of a plot of volume versus number of bead repeats in the chain (see ESI). The van der Waals volumes and  $a_{ii}$  values used in Equations 5-7 are reported in Tables 1 and 2.

The cross-interaction parameters  $\Delta a_{ij}$  in Table 2 show that the strongest repulsion, about  $20 \text{ k}_B\text{T}$ , occurs between water and the two hydrocarbon beads C2 and T as expected. The values compare well with those reported in literature.<sup>25,28,37,44-45</sup> The values of  $\Delta a_{ij}$  for the interactions of the terminal alcohol bead with the hydrocarbon beads, OH-C2 and OH-T, are approximately  $9 \text{ k}_B\text{T}$ , which represents a significant repulsion. The OH bead is well solvated by itself due to H-bonding interactions between the hydroxyl groups, and these interactions are lost when this bead is transferred to a hydrocarbon solvent. The values are similar to those reported in literature: values of  $\Delta a_{ij}$  of  $6 \text{ k}_B\text{T}$  and  $7 \text{ k}_B\text{T}$  were used previously for interactions between OH-C2 and OH-T.<sup>37</sup>

The values of  $\Delta a_{ij}$  for the interactions of the ethylene glycol bead with the hydrocarbon beads, EO-C2 and EO-T, are approximately zero. The major difference between the EO bead and the hydrocarbon beads is the presence of two H-bond acceptor sites on the EO oxygen (Table 1). However, none of these beads have H-bond donor sites, so there are no significant differences in the interactions the beads make with each other. These EO-hydrocarbon cross-interaction parameters in Table 1 differ from those reported in the literature. Because of the limited experimental data on the mutual solubilities of alkanes and oligoethylene glycols,  $\Delta a_{ij}$  was originally estimated to be intermediate in value between the hydrocarbon-hydrocarbon and hydrocarbon-water parameters, and a value of  $6.5 \text{ k}_B\text{T}$  was used in the literature.<sup>26</sup> Attempts to calculate this parameter using COSMO-RS were inconclusive, due to a strong dependence on conformation.<sup>34</sup> Anderson *et al.* used experimental water-octanol partition coefficients to obtain a value of  $3.1 \text{ k}_B\text{T}$  for the EO-hydrocarbon cross-interaction parameter, which is closer to the values in Table 2.<sup>37</sup>

The values of  $\Delta a_{ij}$  for the interactions of the terminal alcohol and ethylene oxide beads with water, W-OH and W-EO, are both negative. The miscibility of water with alcohols and with oligoethylene oxides makes it impossible to determine the values of  $\Delta a_{ij}$  from ex-

perimental solubility measurements. Extrapolation from high temperature measurements on polyethylene oxide-water mixtures gave a value of  $\Delta a_{ij}$  of 1.0–1.5  $k_B T$  for the W-EO interaction. Anderson *et al.* used experimental logP measurements to obtain a value of  $-1.25 k_B T$  for the W-EO interaction, which is consistent with the negative value we calculate. The origin of the negative values of  $\Delta a_{ij}$  in the SSIMPLE calculation is due to the fact that both alcohols and ethylene glycols are H-bond acceptors, and so the H-bonds formed with the water H-bond donors are favorable in the mixtures.

## DPD SIMULATIONS

To test the parametrisation, DPD simulations were performed on linear, non-ionic surfactants belonging to the alkyl ethoxylate family shown in Figure 1; these are generically denoted as  $C_m E_n$  where  $m$  is the number of carbon atoms in the hydrocarbon chain and  $n$  is the number of oxygens in the ethylene glycol chain. In the literature, these compounds are generally described using two types of bead,<sup>26,29,45-47</sup> one for the hydrophobic tail and the other one for the hydrophilic head group, but here we use the more detailed CG description shown in Figure 1.<sup>37</sup> The solvent beads used in the simulations were each composed of two molecules of water. The value of  $R_{ij}$  for the interaction of two water beads was set equal to  $r_c$ , the length unit in DPD, which is in turn set using the mapping number identity proposed by Groot and Rabone:<sup>26</sup>  $\rho N_m v_m = 1$ , where  $\rho$  is the bead density,  $N_m$  (the ‘mapping number’) is the number of water molecules in a water bead, and  $v_m = 30 \text{ \AA}^3$  is the molecular volume of water. With  $N_m = 2$  and dimensionless bead density  $\rho r_c^3 = 3$ , this means that  $r_c = 5.64 \text{ \AA}$ . The correlated cut off distances for all other bead-bead interactions ( $R_{ij}$ ) were taken from Anderson *et al.*<sup>37,42</sup>

In our CG representation of these surfactants (Figure 1), the DPD molecules are linear chains with a stiff harmonic spring potential,

$$U(r) = (1/2) k_b (r_{ij} - r_0)^2 \quad \text{Eq. 8}$$

between connected pairs of beads. We set  $k_b = 150 k_B T$  and choose  $r_0$  to match (approximately) the physical bond lengths as described below. To provide additional chain rigidity we supplement this two-body spring potential with a three-body angular potential,

$$U(\theta) = (1/2) k_a (\theta_{ij} - \theta_0)^2 \quad \text{Eq. 9}$$

where  $k_a = 5 k_B T$  and  $\theta_0 = 180^\circ$ .

For two covalently bonded C2 beads, the equilibrium distance  $r_0$  was set at  $0.39 r_c$ , which gave an average distance during the simulation of  $0.45 r_c$ , equivalent to a bond length of  $2.55 \text{ \AA}$ .<sup>37</sup> The other equilibrium distances ( $r_0$ ) between covalently bonded beads were modified by  $0.1 r_c$  for each heavy atom added or deleted relative to C2, which gives  $0.29 r_c$  for C2-T,  $0.49 r_c$  for C2-EO,  $0.59 r_c$  for EO-EO and  $0.49 r_c$  for EO-OH as in Anderson *et al.*<sup>37,42</sup>

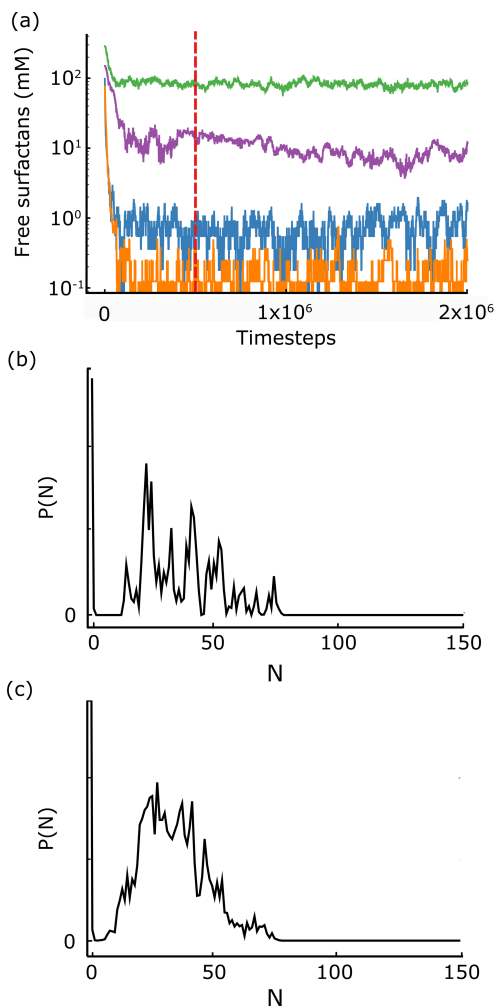
All the simulations were performed in a cubic box of side  $40 r_c$ , containing in total 192,000 beads. Box sizes from  $20 r_c$  to  $40 r_c$  were investigated, but no effect on the value of the calculated CMC was observed (see ESI). Simulations were run for  $(2-4) \times 10^6$  timesteps with a timestep of 0.01 in DPD time units. In the literature, the DPD timescale in this kind of CG representation has been estimated using the diffusion of small molecules,<sup>35</sup> so that one DPD timestep corresponds approximately to 0.5 ps, and our simulation runs correspond roughly to 1–2  $\mu s$ . Simulations were performed using the

DL\_MESO DPD package (version 2.7),<sup>48</sup> and analyzed using a combination of the UMMAP analysis tool<sup>49</sup> and purpose written scripts. Trajectory files were collected every 500 timesteps, and the NVT ensemble was ensured by a commonly used DPD thermostat based on the standard velocity Verlet integration.<sup>50</sup>

DPD simulations were run at 4, 5 and 6% wt in water for all the  $C_m E_n$  surfactants shown in Figure 1. Figure 4 shows examples of the results. Two molecules were considered part of the same supramolecular cluster, if they were closer than the cut-off distance  $R_{ij}$ , and this criterion was used to calculate the number of ‘free’ surfactants as monomers or in submicellar aggregates for each timestep in a simulation. Figure 4a shows the free surfactant concentration for four different surfactants plotted against the number of timesteps. In all cases equilibrium was established between  $1.0 \times 10^5$  and  $2.5 \times 10^5$  timesteps. The cut-off distance criterion was also used to calculate the total number of molecules present within each supramolecular aggregate in each timestep of the simulation. The distribution of supramolecular assemblies was calculated for all timesteps greater than  $5 \times 10^5$  and the populations were summed to obtain the aggregation number distribution ( $P(N)$ ) for each simulation. Figure 4b shows an example of an aggregation number distribution for simulation of  $C_{10} E_6$ . There are clearly two populations. There are a large number of monomers that appear close to the origin, and then there is a clear gap in the trimer to 10-mer region, before a bell-shaped distribution appears with a maximum population around 20. The bell-shaped distribution corresponds to micellar aggregates of various sizes. The results from single simulations can be rather noisy, because the molecules tend to become kinetically trapped in the micellar assemblies. Figure 4b shows that the values of  $P(N)$  obtained from a simulation of  $C_{10} E_6$  are not a simple function of  $N$ . It is possible to obtain a smoother aggregation number distribution by combining multiple simulations, and Figure 4c illustrates the result for  $C_{10} E_6$ .

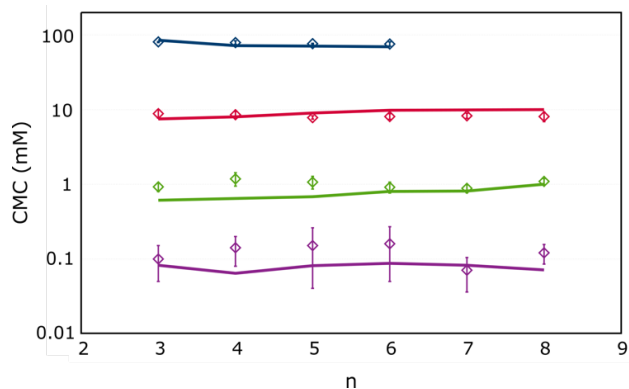
## CRITICAL MICELLE CONCENTRATIONS

The aggregation number distributions were used to calculate CMC values. The minimum number of molecules required for a cluster to be considered a micelle must first be assigned. A variable  $N_{cut}$  is introduced such that clusters with aggregation numbers  $N > N_{cut}$  are identified as micelles, and those with  $N < N_{cut}$  as monomers and submicellar aggregates; the totality of the latter were used to define the free surfactant concentration. For the example shown in Figure 4b, there is a clear gap between the two populations, so choosing a value of  $N_{cut}$  anywhere in the 5–10 range will give the same result. In some simulations, there was overlap between the submicellar and micellar populations, but in these cases, it was still possible identify a sparsely populated intermediate region, where the precise value of  $N_{cut}$  had minimal effect on the calculated CMC values (see ESI). The values of CMC obtained from different simulations of the same surfactant were similar, leading to relatively well-defined values with small error bars. The surfactant concentration used in a DPD simulation can affect the calculated CMC value,<sup>51</sup> but even for simulations run over a wider concentration range (1 to 15% wt of surfactant, see ESI), no significant variations in CMC were found.<sup>52</sup>



**Figure 4.** a) The concentration of free surfactants plotted as a function of timestep for C<sub>6</sub>E<sub>4</sub> (green), C<sub>8</sub>E<sub>5</sub> (violet), C<sub>10</sub>E<sub>6</sub> (blue) and C<sub>12</sub>E<sub>8</sub> (yellow). The red dotted line shows the timestep at which the simulations were considered to have reached equilibrium. All simulations were run at 5%wt. b) The aggregation number distribution for a single simulation of C<sub>10</sub>E<sub>6</sub> at 5%wt. c) The aggregation number distribution for C<sub>10</sub>E<sub>6</sub> calculated by summing the results from nine simulations run at concentrations of 4%, 4.25%, 4.5%, 4.75%, 5.0%, 5.25%, 5.5%, 5.75%, 6.0% wt.

CMC values were calculated for all 22 surfactants by averaging the results from the three different concentrations used in the simulations, 4%, 5% and 6% wt. The results are compared with the corresponding experimentally determined values in Figure 5. The error bars in the calculated CMC values are larger for the C<sub>12</sub> surfactants, due to the small numbers of free surfactants in individual simulations, but in all cases, there is excellent agreement between calculation and experiment. The simulations clearly reproduce the trend that CMC is independent of  $n$ , the length of the ethylene glycol chain, but highly dependent on  $m$ , the length of the hydrocarbon chain. The results are also quantitatively accurate reproducing the order of magnitude drop in CMC for every two CH<sub>2</sub> groups added to the hydrocarbon chain (Stauff-Klevens rule).



**Figure 5.** CMC values for C <sub>$m$</sub> E <sub>$n$</sub>  surfactants plotted as a function of  $n$ . The lines represent the experimental values for each family of surfactants with the same value of  $m$  (blue  $m=6$ , red  $m=8$ , green  $m=10$ , purple  $m=12$ ) and the empty diamonds are the values calculated from DPD simulations.

### MEAN AGGREGATION NUMBERS

For each timestep in a DPD simulation, the mean aggregation number ( $N_{agg}$ ) can be calculated using

$$N_{agg} = \frac{\sum_{N > N_{cut}} N^2 P(N)}{\sum_{N > N_{cut}} N P(N)}. \quad \text{Eq. 10}$$

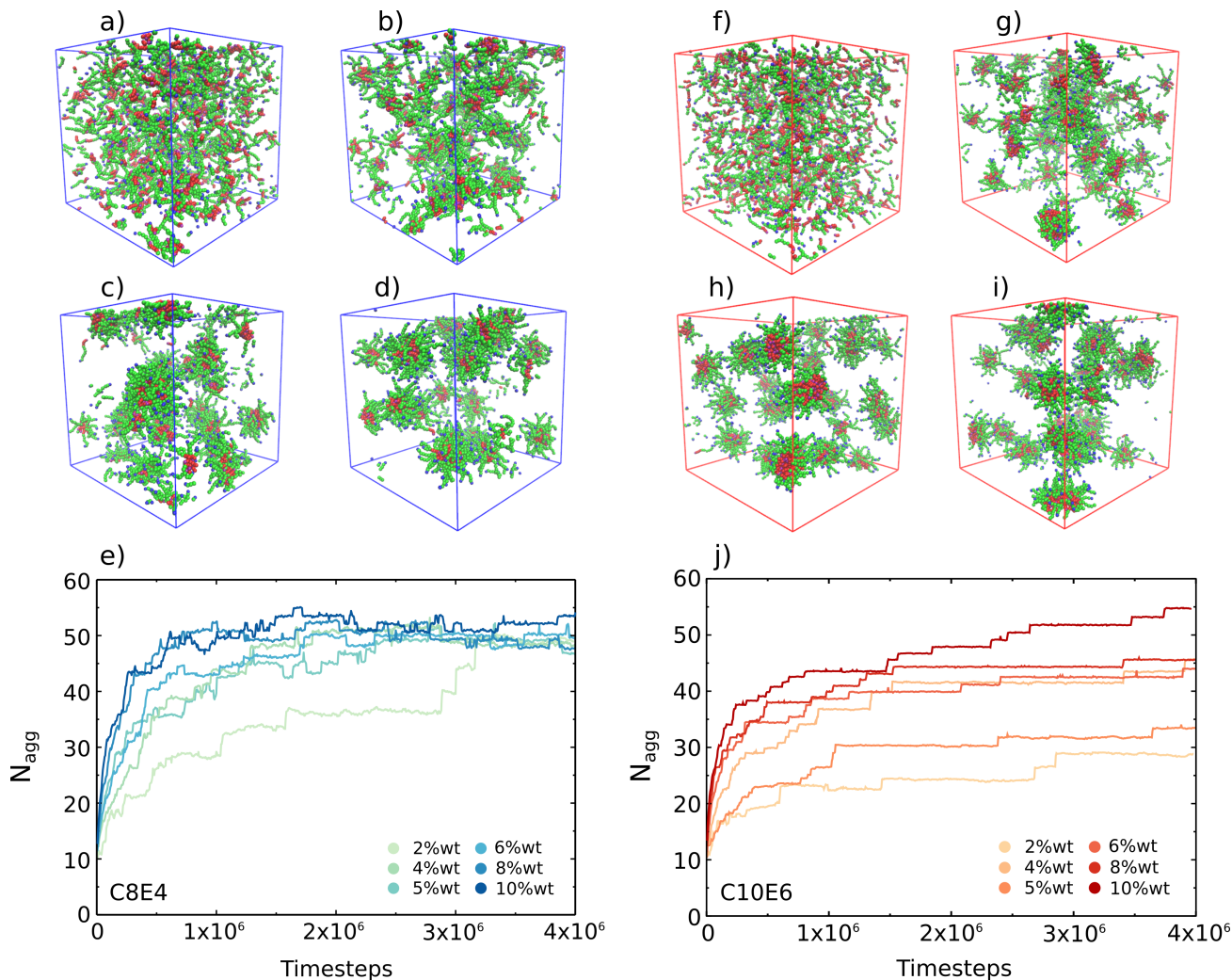
Some authors use different  $N_{cut}$  numbers to determine the values of  $N_{agg}$  and the CMC from the same  $P(N)$  distribution, but here we used the same  $N_{cut}$  for calculation of both values (Table 3).<sup>29,44,53</sup> Consistent values of  $N_{agg}$  were obtained for simulations at different surfactant concentrations between 2 and 10% wt, and the results in Table 3 are quoted as the range of  $N_{agg}$  values obtained from individual simulations. All simulations performed in this work gave spherical micelles with no significant population of other morphologies in agreement with simulations<sup>29,37</sup> and experimental reports in the literature.<sup>54-59</sup> For C<sub>12</sub>E<sub>3</sub>, C<sub>12</sub>E<sub>4</sub>, C<sub>10</sub>E<sub>3</sub>, C<sub>10</sub>E<sub>4</sub>, short-lived interactions of two spherical micelles lead to transient elongated aggregates.<sup>37,60</sup>

Figures 6a-d and 6f-i show snapshots illustrating the evolution of the micelle structure with time for C<sub>8</sub>E<sub>4</sub> and C<sub>10</sub>E<sub>6</sub>. The timescale for equilibration of the  $N_{agg}$  shown in Figures 6e and 6j is much longer than the timescale for equilibration of the monomer concentration shown in Figure 6a. The reason is that the equilibration of micelle size must take place via exchange of molecules between micelles via monomers in solution, and both the number of micelles and the dissociation rate from a micelle are low. Figures 6e and 6j illustrates the effect of surfactant concentration on  $N_{agg}$  equilibration time. For C<sub>8</sub>E<sub>4</sub>, all of the simulations converge to the same value of  $N_{agg}$  (about 50) after  $3 \times 10^6$  timesteps, but the more dilute solutions equilibrate more slowly, because there are fewer micelles. For C<sub>10</sub>E<sub>6</sub>, equilibration is significantly slower, and after  $4 \times 10^6$  timesteps, the values of  $N_{agg}$  for different concentrations have not converged. This behaviour is illustrated in Table 3 where  $N_{agg}$  values are reported after  $2 \times 10^6$  timesteps for all simulations and after  $4 \times 10^6$  timesteps for selected examples. The  $N_{agg}$  values for C<sub>6</sub>E <sub>$n$</sub>  surfactants show no substantial variation between  $2 \times 10^6$  and  $4 \times 10^6$  timesteps, confirming that equilibration occurs rapidly. For C<sub>8</sub>E <sub>$n$</sub> , the  $N_{agg}$  values increase slightly between  $2 \times 10^6$  and  $4 \times 10^6$  steps, but as shown in Figures 6e, equilibrium is reached by  $4 \times 10^6$  timesteps simulations. For C<sub>10</sub>E <sub>$n$</sub>  and C<sub>12</sub>E <sub>$n$</sub> ,

there is a significant difference between the values of  $N_{\text{agg}}$  obtained at  $2 \times 10^6$  and  $4 \times 10^6$  timesteps. Figure 6j shows that the slow equilibration of the more hydrophobic surfactants means that the calculated values of  $N_{\text{agg}}$  are likely to be underestimated.<sup>45</sup>

We note that in principle the mean aggregation number is an increasing function of concentration.<sup>61</sup> This could account for the behavior seen here. Additionally, there are slow processes on ms time scales which are likely to be inaccessible in our  $\mu\text{s}$  simulations.<sup>62</sup> Thus the *number* of micelles may be poorly equilibrated even if the free surfactant concentration has reached a steady state. This obviously impacts the calculation of the mean aggregation number.

Table 3 compares the calculated values of  $N_{\text{agg}}$  with the corresponding experimentally determined values reported by Swope *et al.*<sup>63</sup> Experimental measurement of  $N_{\text{agg}}$  is not straightforward, and the application of different techniques to very broad distributions of micelle size can lead to discrepancies of an order of magnitude in reported values (see  $C_{10}E_5$  and  $C_{12}E_5$  in Table 3). However, the values of  $N_{\text{agg}}$  calculated for the fully equilibrated  $C_6E_n$  and  $C_8E_n$  surfactants agree well with the experimental ranges. For the surfactants with longer hydrocarbon chains,  $C_{10}E_n$  and  $C_{12}E_n$ , the simulations consistently underestimate the value of  $N_{\text{agg}}$ .



**Figure 6.** Evolution of micelle structure in DPD simulations. a-d) Snapshots of  $C_8E_4$  simulation (5% wt) taken after  $5 \times 10^3$ ,  $2 \times 10^5$ ,  $10^6$  and  $4 \times 10^6$  timesteps. e)  $N_{\text{agg}}$  calculated for  $C_8E_4$  plotted as a function of timestep at six different concentrations. f-i) Snapshots of  $C_{10}E_6$  (5% wt) taken after  $5 \times 10^3$ ,  $2 \times 10^5$ ,  $10^6$  and  $4 \times 10^6$  timesteps. j)  $N_{\text{agg}}$  calculated for  $C_{10}E_6$  plotted as a function of timestep at six different concentrations.

**Table 3:  $N_{\text{agg}}$  values from simulation and experiment.**

Surfactant	$2 \times 10^6$ timesteps	$4 \times 10^6$ timesteps	Experiment <sup>61</sup>
C6E3	27-31	28-33	24-57
C6E4	22-24		28
C6E5	20-22	21-23	21-55
C6E6	19-21	19-23	8-12 <sup>64</sup>
C8E3	63-76		
C8E4	43-47	46-54	23-147
C8E5	34-39		17-90
C8E6	31-36	33-41	30-41
C8E7	31-34		
C8E8	29-33	28-34	72 <sup>65</sup>
C10E3	77-97		
C10E4	55-71	58-77	100 <sup>66</sup>
C10E5	40-44		17-172
C10E6	31-41	32-54	66-105
C10E7	28-36		
C10E8	26-32	29-39	46-70
C12E3	85-126		
C12E4	58-76		30 <sup>67</sup>
C12E5	44-53	45-67	112-4460
C12E6	42-46	45-57	100-555
C12E7	36-38		
C12E8	31-37		39-159

## CONCLUSION

A method for calculating the bead interaction parameters required for dissipative particle dynamics (DPD) simulations has been developed. The method is based on *ab initio* calculation of the gas phase molecular electrostatic potential surfaces of the molecular fragments that represent the beads, so the approach should be generally applicable to the coarse graining of any molecular system using DPD. A footprinting algorithm was used to convert the molecular electrostatic potential surfaces into a discrete set of surface site interaction points (SSIPs), and these SSIPs were used in the SSIMPLE algorithm to calculate the free energies of transfer of one bead into a solution of any other bead. The bead transfer free energies were used to obtain the required DPD interaction parameters for all pairwise combinations of different beads. The reliability of this computational approach to determination of accurate DPD parameters was demonstrated using DPD simulations of a range of alkyl ethoxylate surfactants. The simulations reproduce the experimentally determined values of critical micelle concentration and aggregation number well for all 22 surfactants studied. The approach provides a powerful new tool for first principles calculation of DPD parameters and for prediction of the surfactant properties of molecules for which experimental data is not available.

## ASSOCIATED CONTENT

### Supporting Information

Details of the fragment volume calculation, calculated aggregation number distributions for all surfactants, the effect of box size on calculated CMC values, and computational details. The Supporting Information is available free of charge on the ACS Publications website.

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#### Notes

PBW declares a substantive (> \$10k) stock holding in Unilever PLC. All other authors declare no competing financial interest.

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# TOC graphic

