

## MOLECULAR DYNAMICS SIMULATION STUDY OF THE PHASE BOUNDARY FOR COMPLEX COACERVATION BETWEEN POLY(ACRYLIC ACID) AND POLY(N,N-DIMETHYL AMINO ETHYL METHACRYLATE)

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### ABSTRACT

Under certain conditions, the complexation between oppositely charged polyelectrolytes at infinite dilution leads to the formation of a complex coacervate observed in the form of droplets where a polymer-rich (the coacervate) co-exists with a polymer-dilute (the supernatant) phase at thermodynamic equilibrium. Complex coacervates find numerous applications (e.g., in processed food, cosmetics and microencapsulation) due to the small surface tension they exhibit.

The motivation for the present study comes from the experimental work of Spruijt et al.<sup>[1]</sup> who used fluorescent labelled polyelectrolytes to compute the binodal composition of the complex coacervates formed between poly(acrylic acid) (PAA) and poly(N,N-dimethyl amino ethyl methacrylate) (PDMAEMA) of similar chain lengths. The mixtures were prepared at an overall monomer concentration of 0.11 M with 1:1 stoichiometric ratio of charged groups, and experiments were conducted at room temperature and pH=6.5. The aim of this study is to carry out all-atomistic Molecular Dynamics (MD) simulations to predict the binodal composition of such a complex coacervate between PAA and PDMAEMA at the same conditions. In our work, coacervation is studied as a function of salt concentration for PAA chains with degree of polymerization  $N = 20$  monomers and PDMAEMA with degree of polymerization  $N = 17$  monomers, at ambient temperature and neutral pH. The generalized Amber force field (GAFF) with the RESP charge fitting scheme for the calculation of electrostatic interactions was adopted for both PAA and PDMAEMA.

Prior to the estimation of coacervate concentration at co-existence, two different sampling techniques, the Widom Test Particle Insertion method (WTPI) and the Bennet Acceptance Ratio method (BAR), were exploited to compute the excess chemical potential of two water models, SPCE and TIP3P, as a function of temperature ( $T = 300, 310, 320$  K) for the purpose of validating their accuracy. It was observed that the BAR method accurately predicts the excess chemical potential for both (SPCE and TIP3P) models as a function of temperature whereas the WTPI fails; thus, for the subsequent calculations of the chemical potential of the complex coacervates, the BAR method was chosen. To determine the phase boundary of the complex PAA:PDMAEMA coacervate, an iterative procedure was followed which eventually leads to the determination of conditions (polyelectrolyte concentrations) for which the chemical potential of salt ions and solvent in the two phases (supernatant and coacervate) become equal. In this work, we discuss the binodal composition of the PAA:PDMAEMA coacervates computed from this all-atom MD study, and how it compares with the experimental data of Spruijt et al.,<sup>[1]</sup> the mean-field model of Voorn and Overbeek,<sup>[2]</sup> and the coarse-grained simulations of Andreev et al.<sup>[3]</sup>

### INTRODUCTION

The phenomenon of complex coacervation has attracted a great deal of attention in the last decade as it is believed that the coacervate material could be of prominent importance for the design of novel materials favouring applications in the pharmaceutical and food industries as microencapsulates for drugs, aromas and flavours.<sup>[4-7]</sup> A noteworthy study carried out by Dompé and co-workers<sup>[8]</sup> revealed that a complex coacervate material composed of thermo-responsive domains could be the foundation for the development of an underwater adhesion material, having controlled cohesive properties stimulated by external environmental conditions.

The term *complex coacervate* was first introduced by Bungenberg de Jong in a study of mixtures of gum Arabic and gelatin.<sup>[9]</sup> The mixing of two oppositely charged polyelectrolytes at infinite dilution resulted in the

formation of polyelectrolyte complexes (PECs). Under certain circumstances, the complexation between polycation and polyanion may drive the formation of complex coacervates, a phenomenon manifested in the form of droplets. In this case, two phases are distinct; a polymer-rich and a polymer-dilute phase which co-exist in equilibrium.<sup>[10]</sup>

Shortly after Bungenberg de Jong's pioneering study,<sup>[9]</sup> several theoretical studies<sup>[2, 11]</sup> appeared in an effort to describe the mechanisms that govern complex coacervation. The first such notable theoretical study was that of Overbeek and Voorn<sup>[2]</sup> which suggests that the phenomenon of coacervation occurs due to the combination of electrostatic interactions and mixing entropy terms. In a later study carried out by Veis and co-workers,<sup>[12]</sup> the idea of the formation of soluble complexes prior to coacervation was introduced. The influence of variety of parameters (such as of the ionic strength, stoichiometry, pH, polymer chain length, total polymer concentration and temperature) towards the formation of coacervate material have lately been identified experimentally.<sup>[13-16]</sup> Still nowadays there is a lack of a theoretical model capable of considering all parameters affecting the formation of coacervate material.

The prediction of coacervate composition has only been recently computed by Monte Carlo<sup>[17]</sup> and Molecular Dynamics simulations.<sup>[3, 18]</sup> The goal of the present work is to predict the binodal composition of the coacervate phase formed between PAA and PDMAEMA by means of all atomistic MD simulation, and compare our findings against theory<sup>[2]</sup> and experiment.<sup>[1]</sup>

The rest of our work is organized as follows. In section 2, the description of the various computational techniques to calculate the excess chemical potential is presented. In section 3, the validation of these techniques to accurately compute the excess chemical potential of water and salt for various temperature in comparison to well-accepted reference values is presented. In addition, the procedure of estimating the coacervation composition is illustrated and the comparison of our predictions against theory and experiment is presented. In section 4, the final conclusions of our work are presented.

## METHODOLOGY APPROACH

The chemical potential is an important thermal property for simulating phase equilibrium. In the canonical ensemble (nVT) is defined as:

$$\mu = \left( \frac{\partial A}{\partial N} \right)_{T,V} \quad (1)$$

Several computational methods exist to estimate the chemical potential of a system such as the i) Widom Test Particel Insertion (TPI) method, ii) particle deletion method, iii) free energy perturbation (FEP) methods and iv) thermodynamic integration (TI) method.

In 1963, Widom proposed a scheme to measure the chemical potential in a system using trial particle insertions.<sup>[19]</sup> In this case, the particle number is discrete and thus the above equation becomes:

$$\mu = \left( \frac{\partial A}{\partial N} \right)_{T,V} = \frac{A(N+1, V, T) - A(N, V, T)}{N+1 - N} = A(T, V, N+1) - A(T, V, N) \quad (2)$$

The free energy (for nVT statistical ensemble) can be computed from:

$$A = -k_B T \ln Q \quad (3)$$

Whereas  $k_B$  J mol<sup>-1</sup> K<sup>-1</sup> is the Boltzmann constant,  $T$  K the temperature and  $Q$  the canonical partition function which is defined as (for nVT statistical ensemble):

$$Q(N, V, T) = \frac{V^N}{N! \Lambda^{n_d N}} \int_0^V \exp(-\beta U(\mathbf{r}^N)) d\mathbf{r}^N \quad (4)$$

Here  $V$  is the volume,  $\Lambda = h / \sqrt{2\pi m k_B T}$  the thermal wavelength,  $n_d$  the dimension of the system,  $\beta$  the inverse thermal energy and  $U$  the interaction potential. Combining the above expressions, Eq. 2 leads to:

$$\mu = k_B T \ln \frac{N+1}{V} \Lambda^{3N} - k_B T \ln \langle \exp(-\beta \Delta U) \rangle \quad (5)$$

which expresses the chemical potential as the sum of an ideal part  $\mu^{ig} = k_B T \ln \frac{N+1}{V} \Lambda^{3N}$  and an excess part  $\mu^{ex} = -k_B T \ln \langle \exp -\beta \Delta U \rangle$ .

While the TPI method is very efficient, it is only applicable for small solutes in systems with low density.<sup>[19]</sup> As reported by Pohorille and co-workers,<sup>[20]</sup> successful placements of a test particle may be complicated, and placements with favourable Boltzmann factor scores may be rare. In the case for very dense systems, an inserted particle almost always produces a core overlap which results in a large change in  $\Delta U$ .

To overcome the limitation of the TPI method, FEP methods are explored. These were introduced in the 1950s by Zwanzig, the basic idea being to compute the free energy between a reference state and some perturbed state.<sup>[21]</sup> The perturbed state may include an additional particle, a slightly different potential energy function, or a small change in temperature. The goal of the FEP methods is to calculate the free energy difference between the reference system and the target system characterized by a Hamiltonian  $H_1$   $\mathbf{r}, \mathbf{p}$  :

$$H_1 \mathbf{r}, \mathbf{p} = H_0 \mathbf{r}, \mathbf{p} + \Delta H \mathbf{r}, \mathbf{p} \quad (6)$$

The fundamental FEP formula for the forward,  $0 \rightarrow 1$  transformation reads:

$$\Delta A = -\frac{1}{\beta} \ln \langle \exp[-\beta \Delta H \mathbf{r}, \mathbf{p}] \rangle_0 \quad (7)$$

If the kinetic term cancels out (same masses) then the above equation gives the Zwanzig formalism/relationship:

$$\Delta A = -\frac{1}{\beta} \ln \langle \exp -\beta \Delta U \rangle_0 \quad (8)$$

Since the FEP equation is asymmetric, it can give the free energy based on an average in only one of the ensembles here state 0. A similar derivation gives an expression if we use state 1 as the average ensemble:

$$\Delta A = \frac{1}{\beta} \ln \langle \exp -\beta \Delta U \rangle_1 \quad (9)$$

Perturbation-based methods include a broad range of techniques such as the Bennet Acceptance Ratio (BAR), the Deletion Exponential Averaging (DEXP), and the Insertion Exponential Averaging (IEXP) methods. DEXP and IEXP are based on the exponential averaging scheme of the difference of the potential energies  $\Delta U_{ij}$  between two adjacent states  $i$  and  $j$  over one of the ensembles – the so called Zwanzig relationship (see eq. 8). Depending on the direction of the transformation, the process can be interpreted as either «deletion» or «insertion». As reported by Wu and co-workers,<sup>[22]</sup> DEXP proceeds in the direction of increasing entropy (turning on intermolecular interactions between molecule and environment), while IEXP proceeds in the direction of decreasing entropy (turning off intermolecular interactions between molecule and environment).

Alternate approximations for the free energy change may be conducted when using methods based on the Zwanzig relationship depending on the direction of the transformation. These discrepancies originate from under-sampling in the tail regions of the  $\Delta U_{ij}$  -distributions, resulting in biased free energy estimates. BAR method uses samples of the potential energy in both  $i$ -to- $j$  and  $j$ -to- $i$  directions to obtain a provably minimum variance estimate of the free energy difference. This is mathematically expressed as

$$\Delta A = -k_B T \ln \frac{\langle f U_1 - U_0 \rangle_{\lambda_0}}{\langle f U_0 - U_1 \exp[-\beta U_1 - U_0] \rangle_{\lambda_1}} \quad (10)$$

Instead of evaluating the difference in the free energy between subsequent states, another class of methods aims at estimating the derivative of the potential energy function with respect to a coupling parameter  $\lambda$  for a system from a simulation average. This method is known as the Thermodynamic Integration (TI) method and is mathematically expressed as<sup>[23]</sup>

$$\Delta A = \sum_{i=1}^n W_i \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_{\lambda_i} \quad (11)$$

where  $W_i$  are weighting factors that depend on the numerical integration scheme used. In this work, we implement the TI-1 and TI-3 methods which differ in how they interpolate between data points for integration. TI-1 uses the trapezoidal rule (a first-order polynomial) while TI-3 a (natural) cubic spline.<sup>[23]</sup>

## RESULTS AND DISCUSSION

### Method validation

Prior to the investigation of the phase equilibrium, a systematic validation of several of the above-mentioned methods was carried out to ensure their capability to accurately estimate the excess chemical potential. To this, we designed a system consisting of 1000 water molecules and a system consisting of 1000 water molecules and 1 salt molecule (KCl) in order to study the excess chemical potential of water and salt at three different temperature ( $T = 300, 310$  and  $320\text{K}$ ).

It is revealed that the TPI method fails to predict the excess chemical potential of water with temperature whereas the BAR method compares very well with EoS.<sup>[24]</sup> Thus, decided to employ the BAR method for predicting the binodal coacervate composition formed from the complexation between PAA and PDMAEMA in aqueous solution.

### Complex coacervation

To study the phase equilibrium of the system consisting of PAA and PDMAEMA, we followed an iterative procedure to equate the total chemical potential of the solvent (water) and salt ions in the two phases. So far we have completed this iterative process for PAA and PDMAEMA with chain length  $N = 20$  only at salt concentrations:  $c_{\text{salt}} = 0.2\text{M}$  and  $c_{\text{salt}} = 0.3\text{M}$ . The coacervate composition was found at total polymer concentration  $c_p = 1.8\text{M}$  and  $c_p = 1.4\text{M}$  for the systems consisting of  $c_{\text{salt}} = 0.2\text{M}$  and  $c_{\text{salt}} = 0.3\text{M}$ , respectively. It is found that the coacervate composition predicted from our MD study compares very favourably with the VO theory,<sup>[2]</sup> recent experimental data and coarse-grained MD simulation studies.<sup>[1, 3]</sup>

## CONCLUSION

The coacervate composition predicted from our MD study is found to be in excellent agreement with the VO theory<sup>[2]</sup> and recent experimental and MD (coarse-grained model employed) studies<sup>[1, 3]</sup> for two systems with salt concentration  $c_{\text{salt}} = 0.2\text{M}$  and  $c_{\text{salt}} = 0.3\text{M}$ , respectively. The next step is to study the coacervation composition for a system consisting of PAA and PDMAEMA with higher molecular length,  $N = 50$  and  $100$ , at various salt concentrations.

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