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1 Introduction

Oppositely charged species can undergo an associative phase separation in aqueous, salt solution in a process known as complex coacervation.¹ Discovered in 1929, complex coacervation was originally observed in biomacromolecules such as proteins and polysaccharides,² and found use as a viscosity modifier and encapsulant in food and other personal care products.^{3–5} Emerging work in the polymer community has focused on the ability of coacervation to drive self-assembled structures,^{6–11} and concomitantly the biophysics community has begun to realize the importance of coacervation in intrinsically disordered proteins and membraneless organelles.^{12–15} Despite this long-standing utility, it remains difficult to provide a comprehensive, physical description of the coacervation process.^{16,17}

The primary challenge of developing a theoretical description of complex coacervation stems from correctly describing the nature of the electrostatic attractions between all the species in the system. In polymeric complex coacervates, the system is comprised of a polycation, polyanion, cation, anion, and water. The first theoretical prediction of coacervation is known as Voorn– Overbeek (VO) theory,^{18,19} which describes the four charged species using a Debye–Hückel²⁰ term that captures the attraction between the oppositely-charged species. This competes against

Transfer matrix theory of polymer complex coacervation

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Oppositely charged polyelectrolytes can undergo a macroscopic, associative phase separation in solution, *via* a process known as complex coacervation. Significant recent effort has gone into providing a clear, physical picture of coacervation; most work has focused on improving the field theory picture that emerged from the classical Voorn–Overbeek theory. These methods have persistent issues, however, resolving the molecular features that have been shown to play a major role in coacervate thermodynamics. In this paper, we outline a theoretical approach to coacervation based on a transfer matrix formalism that is an alternative to traditional field-based approaches. We develop theoretical arguments informed by experimental observation and simulation, which serve to establish an analytical expression for polymeric complex coacervation that is consistent with the molecular features of coacervate phases. The analytical expression provided by this theory is in a form that can be incorporated into more complicated theoretical or simulation formalisms, and thus provides a starting point for understanding coacervate-driven self-assembly or biophysics.

a Flory-Huggins entropy term that favors mixing,²¹ leading to an expression for the free energy F_{VO} :^{18,19,22}

$$\frac{F_{\rm VO}}{Vk_{\rm B}T} = \sum_{i} \frac{\phi_{i}}{N_{i}} \ln \phi_{i} - \alpha \left(\sum_{i} \sigma_{i} \phi_{i}\right)^{3/2}$$
(1)

Here, ϕ_i is the volume fraction for all species *i*, α is a term related to the strength of the electrostatic interaction, σ_i sets the proportionality between the number of charges and the volume fraction, and N_i is the degree of polymerization for all species ($N_i = 1$ for small molecules).^{18,19,22} This simple expression has been found to fit well to experimental data;²² however, it is now appreciated that the fit parameters (*i.e.* α , σ_i) are unphysical.^{23–26} A dispersive χ contribution is typically also included.²²

Voorn–Overbeek theory suffers from a number of deficiencies. The Debye–Hückel term does not differentiate between charges on the polymer chains or in the salt, and similarly does not account for the connected nature of the polymer chains.¹⁶ Furthermore, the standard salt and polymer concentrations in coacervates ($\sim 100 \text{ mM-1 M}$)^{22,27,28} are well above where the assumptions associated with Debye–Hückel break down. As such, if VO is expected to work, it should be in the limit of low salt and low linear charge density polymers.¹⁶ Random Phase Approximation (RPA)^{24,29–31} and field theoretic methods^{32–34} have been extensively used to move beyond these limitations, by including connectivity or finite size. Nevertheless, many of these field theory-based methods remain unable (or impractical) to resolve the molecular structure that is characteristic of high charge-density polymers.^{9,31}

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Computational efforts have, for the most part, focused on complexation between pairs of polyelectrolytes.^{35–38} These systems point to an alternative physical explanation related to 'counterion release', which has often driven the conceptual intuition of experimentalists in the field of complexation and biophysics. In contrast to VO theory, which does not include connectivity between charges, counterion release relies on the high charge density of the polyelectrolyte chains. The large electrostatic energy of the connected charges is relieved by localizing counterions or salt ions of the opposite charge, in a process known as 'counterion condensation'.³⁹ Two nearby polyelectrolytes of opposite charge condense upon each other during complexation, so that the previously condensed counterions are no longer localized. The gain in translational entropy drives complexation.

Simulation and liquid state theory investigations by the authors have demonstrated results consistent with counterion condensation and release,^{23,25} and thus in agreement with experimental thermodynamic studies.40 These results underscore the importance of molecular structure on the phase behavior of coacervates, with features such as charge spacing and excluded volume playing a key role.^{23,25} Furthermore, values from coacervate simulations can be used to parameterize VO theory, demonstrating the extent to which it yields unphysical predictions.²⁵ Despite the relevance of the counterion condensation mechanism to coacervation, there have been very few works that have incorporated these ideas into a theory of coacervation. Ou and Muthukumar,35 for example, have developed theory to understand counterion release in the context of complexation between a single polyanion and single polycation chain. This does not portray bulk coacervates where any given chain interacts with many other neighbors; however, the insights from this work have had a strong influence on experimental intuition and further theory development. For example, there have been efforts at extending this picture to coacervates by Wang and Schlenoff via analogies to 'doping' from a solidlike complex state.41,42 Perhaps the most complete manifestation of these ideas in a theory has been by Salehi and Larson,²⁶ who recently developed a theory that includes counterion condensation and release via 'effective' chemical reactions parameterized directly from experimental measurements. However, there remains a need for a theory that directly connects counterion condensation and release to both molecular structure and coacervate phase behavior.

In this paper, we present a new theory based on the context of a single chain in a field of its neighbors. Coacervate-forming systems typically possess a high density of charged species, and thus correlations in these systems are effectively short-range with neighboring molecules playing the most significant role in the thermodynamics of association.²⁵ Our theory leverages this observation, which leads to a counterion condensation picture that is consistent with the local structure of a coacervate as measured by simulation. The primary result of this paper is a straightforward analytical expression for the system free energy. We demonstrate that this result predicts behaviors that standard field theories do not exhibit,^{16,23,25} such as the preferential partitioning of salt to the supernatant phase, and are unable to resolve, such as the effect of local charge spacing.

2 Simulation

We use simulation to inform and test our theory,⁴³ due to previous success in qualitatively comparing simulation results to experiment.²⁵ Indeed, most of the features we seek to explain with our theory (local structure and correlations) are in simulation without approximation, albeit with non-negligible computational cost. The common limitation with both will be our invocation of the restricted primitive model (RPM) that does not resolve atomistic detail.^{44,45} The RPM treats ions as hard-sphere beads that can be connected to form polyelectrolytes, all of which interact *via* Coulomb potentials in a continuum medium with the solvent dielectric constant.

Limitations associated with RPM are well-known,⁴⁶ such as the neglect of specific ion effects and the nuances of water structure in aqueous systems. This prevents quantitative prediction. RPM simulations also neglect potential variations in the relative dielectric constant, which has been shown to vary at large concentrations of salt or polymer.^{47–49} Dielectric constant plays an especially large role in polyelectrolytes in the melt state,^{50,51} and can become important in solution.^{52,53} We justify neglecting this possible effect by noting the high concentration of water in typical coacervate systems ($\sim 60-80\%$).²² Previous RPM simulations have shown reasonable agreement with experimental measurement,²⁵ to the extent that it is possible to qualitatively match trends due to architecture and sequence.

Our simulation approach is to use Monte Carlo (MC) simulations to provide thermodynamic inputs to a field theory that can predict coacervation. This method was developed by Lytle *et al.*, and is an almost exact match to Gibbs ensemble calculations based solely on MC simulation.⁵⁴

2.1 RPM model of coacervation

MC simulations are performed in an *NVT* ensemble of $N_P \times n_{P+}$ polycation monomers, $N_P \times n_{P-}$ polyanion monomers, n_+ cations, and n_- anions. These species are at positions \mathbf{r}_i^{α} , where *i* is the index specifying the monomer or ion and α specifies the type (P+, P-, +, - for polycation, polyanion, cation, and anion). Polycations and polyanions both have degree of polymerization N_P . Water is modeled as an implicit solvent with a relative dielectric constant, $\varepsilon_r = 78.5$. See Fig. 1a for a schematic of our model. All beads have a hard core diameter σ . Monomers and ions are explicit, and contribute to the overall system energy *U* given by:

$$U = U_{\rm HS} + U_{\rm E} + U_{\rm B} + U_{\theta} \tag{2}$$

 $U_{\rm HS}$ is the hard sphere energy that prevents overlap of the beads:

$$U_{\rm HS} = \sum_{\alpha,\beta} \sum_{i,j} u_{\rm HS} \left(r_{ij}^{\alpha,\beta} \right) \tag{3}$$

Here, $r_{ij}^{\alpha,\beta} = |\mathbf{r}_i^{\alpha} - \mathbf{r}_j^{\beta}|$ is the distance between beads *i* and *j* on species α and β , and the individual pair potential u_{HS} is given by:

$$u_{\rm HS}\left(r_{ij}^{\alpha,\beta}\right) = \begin{cases} \infty & r_{ij}^{\alpha,\beta} < \sigma \\ 0 & r_{ij}^{\alpha,\beta} \ge \sigma \end{cases}$$
(4)

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Fig. 1 (a) Schematic of the simulation model used in this paper. The RPM is used, with all hard-sphere particles of diameter σ and electrostatic interactions between all charged species $U_{\rm E}$. Polymers are connected charges with a bonding potential $U_{\rm B}$ and a bending potential U_{θ} . (b) Simulation snapshot of a coacervate phase using our model. A method known as Widom insertion measures the energy change associated with adding pairs of charged particles into a simulation box, yielding excess chemical potentials that can be integrated to calculate $f_{\rm EXC}$.

 $U_{\rm E}$ is the charged Coulomb potential:

$$U_{\rm E} = \frac{1}{2} \sum_{\alpha,\beta} \sum_{i,j} \frac{q_{\alpha} q_{\beta}}{4\pi \varepsilon_0 \varepsilon_{\rm r} r_{ij}^{\alpha\beta}} \tag{5}$$

where q^{α} is the per-bead charge of species α and ε_0 is the vacuum permittivity. Ewald summation is used to calculate electrostatic interactions in the simulation. $U_{\rm B}$ is the bonding potential between beads along the polymer chains:

$$U_{\rm B} = \sum_{\alpha=P+,P-} \sum_{i} {}^* u_{\rm B} \left(r_{i,i-1}^{\alpha,\alpha} \right) \tag{6}$$

We constrain α to only be along connected polymer chains, and the asterisk in the second summation indicates that we omit terms where *i* mod *N* = 0. The pair potential $u_{\rm B}$ is given by:

$$u_{\rm B}\left(r_{i,i-1}^{\alpha,\alpha}\right) = \begin{cases} 0 & \Delta\sigma \le r_{i,i-1}^{\alpha,\alpha} < \Delta\sigma + 0.1\sigma\\ & \\ \infty & \text{otherwise} \end{cases}$$
(7)

Here we can adjust the spacing by a factor of Δ . An angle potential contribution U_{θ} is applied to the polymer chains:

$$U_{\theta} = \sum_{\alpha=P+,P-} \sum_{i} {}^{**} u_{\theta} \left(r_i^{\alpha}, r_{i-1}^{\alpha}, r_{i-2}^{\alpha} \right)$$
(8)

The double asterisk in the second summation indicates that we omit terms where $i \mod N = 0$ or 1. The pair potential u_{θ} is given by:

$$u_{\theta}(r_{i}^{\alpha}, r_{i-1}^{\alpha}, r_{i-2}^{\alpha}) = \frac{\kappa_{\theta}}{2} \theta_{i,i-1,i-2}^{2}$$
(9)

 κ_{θ} is a constant determining the strength of the bond angle potential, and $\theta_{i,i-1,i-2}$ is the angle between the adjacent bond vectors.

For all simulations, we choose $\sigma = 4.25$ Å and $\kappa_{\theta} = 3.3k_{\rm B}T$, and consider 12 chains of $N_{\rm P} = 100$. We ran multiple simulation box sizes to check that we had no finite box size effects. We use translational MC moves, and run simulations for at least 1×10^7 cycles to reach equilibrium.

2.2 Using MC to predict phase behavior

We use Widom insertion to obtain the excess chemical potentials $\mu_{\text{EXC}}^{\alpha}$ for all species α in the system. Standard techniques are used, including joint insertion of positively and negatively charged species to ensure electroneutrality, and the use of chain-end monomer addition to calculate the per-monomer $\mu_{\text{EXC}}^{\alpha}$ for $\alpha = P+$, P-.⁵⁵ The entire set of excess chemical potentials was tabulated at a number of values of ϕ_{S} and ϕ_{P} , and thermodynamic integration was used to calculate the excess free energy from a reference state ϕ_{S}^{α} and ϕ_{P}^{α} :

$$f_{\text{EXC}}(\phi_{\text{S}}, \phi_{\text{P}}) = \int_{\phi_{\text{S}}^{0}, \phi_{\text{P}}^{0}}^{\phi_{\text{S}}, \phi_{\text{P}}^{0}} \mu_{\text{EXC}, \text{S}} \left(\phi_{\text{S}}^{'}, \phi_{\text{P}}^{0}\right) d\phi_{\text{S}}^{'} + \int_{\phi_{\text{S}}, \phi_{\text{P}}^{0}}^{\phi_{\text{S}}, \phi_{\text{P}}} \mu_{\text{EXC}, \text{P}} \left(\phi_{\text{S}}, \phi_{\text{P}}^{'}\right) d\phi_{\text{P}}^{'}$$
(10)

This excess free energy, which is informed from simulation, can be incorporated into a free energy expression:

$$\frac{\mathscr{F}_{\rm sim}}{Vk_{\rm B}T} = \frac{\phi_{\rm P}}{N_{\rm P}} \ln \phi_{\rm P}/2 + \phi_{\rm S} \ln \phi_{\rm S}/2 + \phi_{\rm W} \ln \phi_{\rm W} + f_{\rm EXC}(\phi_{\rm P}, \phi_{\rm S})$$
(11)

We numerically calculate the two phases that minimize this free energy expression to calculate the simulation binodals. It has been shown that this method for calculating binodals matches almost exactly with more computationally demanding techniques such as Gibbs ensemble Monte Carlo.⁵⁴ More detailed discussion of this method can be found in Lytle, *et al.*⁵⁴

3 Theory

3.1 Multicomponent charge condensation along a test chain

We consider a test polyelectrolyte in the bulk of a coacervate phase, with monomers *i* that proceed from i = 1 to i = N. We will explore the environment along the contour of this chain, where the oppositely-charged species can 'adsorb' to the linear

test molecule. Accounting for these adsorbing molecules will enable calculation of the free energy of interaction of a polyelectrolyte with its surroundings. The counterion C and the oppositely-charged polymer P are possible adsorbing species. As the contour coordinate of the chain is traversed, we further distinguish between an initial polymer unit in a run of adsorbed monomers, P', and the subsequent monomers P that are adjacent along the adsorbed chain (i.e. not from a different, competing chain). Fig. 1 schematically demonstrates these distinctions, and shows that each adsorbed species (C, P', and P) are each associated with a single monomer along the test chain. There is also a possibility that there are no species that are nearby a given monomer within an arbitrary cutoff $r_{\rm C}$, which we designate as 0. We note that this is relatively infrequent, because we focus on applying this model under conditions where most monomers are 'paired'. This is a limitation of our approach, which we expect will be most accurate in the high charge-density limit where counterion condensation is strong.

3.2 Interaction free energy

The system of interest is the immediate volume surrounding the test chain, which has an open boundary to the oppositely charged chains and counterions in the environment. For now, we consider the polymer and salt species in the environment to be at chemical potentials $\mu_{\rm P}$ and $\mu_{\rm S}$ respectively. Similarly, we assign a penalty ε for not having a paired charge (0) adjacent to a monomer on the test chain. This phenomenological parameter is related to the entropic cost associated with having a charged monomer without a nearby pair within the arbitrary distance $r_{\rm C}$. This is left as a fit parameter in our model, and we observe that it remains unchanged over all conditions considered in this paper. We write the grand canonical partition function for a test chain with *N* monomers by:

$$\Xi(N) = \sum_{\{s_i\}} \exp\left[-\beta \sum_{j}^{N} \left(\varepsilon \delta_{s_j,0} - \mu_{\mathbf{P}} \delta_{s_j,\mathbf{P}'} - \mu_{\mathbf{S}} \delta_{s_j,\mathbf{C}^-} - k_{\mathbf{B}} T \delta_{s_{j-1},\mathbf{P}'} \delta_{s_j,\mathbf{P}} \ln 2E - k_{\mathbf{B}} T \delta_{s_{j-1},\mathbf{P}} \delta_{s_j,\mathbf{P}} \ln E\right)\right]$$
(12)

Here, the indices *j* denote locations along the chain, each with a state $s_j = C$, P, P', 0 that represents the immediate environment. The asterisk on the sum denotes the constraint that it is not possible to have adjacent sites where $s_j = P$ and $s_{j-1} = C$ or $s_j = P$ and $s_{j-1} = 0$. *E* represents a single-particle partition function associated with the confinement of adsorbed monomers after the first monomer has been adsorbed; we initially set this to be E = 1, which sets the otherwise arbitrary reference states of the chemical potential terms μ_P , μ_S , and the energy ε . The factor of 2 in the ln 2*E* term is associated with the degeneracy of choosing a direction to adsorb the second monomer P after initially adsorbing the chain P'. This contrasts with the ln *E* term, which is due to the propagation of the adsorbed chain (P to P). In this case, continuation must be along a direction along the adsorbing chain already determined by the initializing P' to P step.

This partition function is more concisely written using the transfer matrix formalism. Here, we note that the partition function at a number of monomers N + 1 is related to the partition function of a chain with *N* monomers. For example, if the last monomer in the chain is $s_{N+1} = P$, then the partition function $\Xi(N + 1, s_{N+1} = P)$ can be written as:

$$\Xi(N + 1, s_{N+1} = P) = \Xi(N, s_N = P)e^{-\beta[-k_B T \ln E]} + \Xi(N, s_N = P')e^{-\beta[-k_B T \ln 2E]}$$
(13)

The bracketed terms in the exponential factors correspond are deliberately written to correspond to contributions to the sum in the exponent of eqn (12). Similar relationships can be written for all possible values of s_{N+1} . We generalize this by representing the exponential factors (such as those in eqn (13)) in matrix form; we define the contribution to the partition function for an adsorption state s_i at monomer 'site' *i* given the adsorption state s_{i-1} at the previous monomer site i - 1 using a matrix $\mathbf{M}(s_i, s_{i-1})$:

$$\mathbf{M}(s_{i}, s_{i-1}) = \begin{bmatrix} \mathbf{CC} & \mathbf{CP} & \mathbf{CP}' & \mathbf{C0} \\ \mathbf{PC} & \mathbf{PP} & \mathbf{PP}' & \mathbf{P0} \\ \mathbf{P'C} & \mathbf{P'P} & \mathbf{P'P'} & \mathbf{P'0} \\ \mathbf{0C} & \mathbf{0P} & \mathbf{0P'} & \mathbf{00} \end{bmatrix} = \begin{bmatrix} A & A & A & A \\ \mathbf{0} & E & 2E & \mathbf{0} \\ B & B & B & B \\ D & D & D & D \end{bmatrix}$$
(14)

The first version of the matrix describes the states $s_i = C, P, P', 0$ and $s_{i-1} = C, P, P', 0$, pairs of which contribute to the partition function. The second version of the matrix assigns each element to the factors $A = e^{\bar{\mu}s}$, $B = e^{\bar{\mu}p}$, $D = e^{-\bar{\epsilon}}$, and E = 1 where tildes denote normalization by the thermal energy $k_{\rm B}T$. The partition function can be rewritten using this matrix:

$$\Xi = \psi^T \mathbf{M}^N \psi \tag{15}$$

where the vectors ψ are comprised of ones. For sufficiently large *N*, the largest eigenvalue of the matrix **M**(ξ) dominates this partition function, and has an analytical form:

$$\Xi = \xi^{N}$$

$$= \left[\left(A + B + D + E + \sqrt{(A + B + D + E)^{2} - 4E(A - B + D)} \right) / 2 \right]^{N}$$
(16)

This partition function is directly related to a free energy of interaction between *N* monomers of a coacervate chain and its surroundings:

$$\mathcal{F}_{\text{int}} = -k_{\text{B}}T\ln\Xi = -Nk_{\text{B}}T\ln\left[A + B + D + E\right]$$
$$+\sqrt{(A + B + D + E)^2 - 4E(A - B + D)} + Nk_{\text{B}}T\ln2$$
(17)

The last term is simply an additive constant that we will neglect for the rest of this paper. This equation is a function of μ_S , μ_P , and ε that determine *A*, *B*, *D*, and *E* respectively. These parameters connect this tagged polymer chain to the surrounding environment.



Fig. 2 Our theoretical model uses a coordinate that is along the contour of a test polymer (top, dark orange). We assign to each monomer of this test polymer a 'nearest neighbor' particle of the opposite charge, which can be a counterion C, a polymer P or P' (middle). It is also possible that no nearby neighbor we consider the monomer unpaired 0, using a cutoff $r_{\rm C}$ (red circles). These assignments are converted into a sequence (bottom) describing the state of the test particle; our model of interactions is built around determining the free energy associated with the many sequence possibilities.

3.3 Chain environment

We assume a straightforward expression for the chemical potentials, $\tilde{\mu}_{\rm S} = \tilde{\mu}_{\rm S}^0 + \ln \phi_{\rm S} = \ln(A_0\phi_{\rm S})$ and $\tilde{\mu}_{\rm P} = \tilde{\mu}_{\rm P}^0 + \ln \phi_{\rm P} = \ln(B_0\phi_{\rm P})$, to be from a new chain if it is more than 3 monomers from the previous adsorbed monomer.

Fig. 2 shows a characteristic sequence description of the test chain environment. We quantify the statistics of this sequence by calculating the conditional probability of observing an adsorbed species s_i at monomer i given that we previously had an adsorbed species s_{i-1} at monomer i - 1, $p(s_i|s_{i-1})$. These conditional probabilities are directly calculable from the transfer matrix elements:

$$p(s_i|s_{i-1}) = \frac{\mathbf{M}(s_i, s_i - 1)}{\sum\limits_{s_i} \mathbf{M}(s_i, s_{i-1})}$$
(18)

As such, our predictions can be compared to simulation results and thus to molecular structure. For example, we can calculate $p(C|P) = A/(A + E + B + D) = A_0\phi_S/(A_0\phi_S + B_0\phi_P + e^{-\tilde{\epsilon}} + 1)$. Fig. 3 shows how a number of these conditional probabilities compare between the theory and the simulation as ϕ_S is changed at constant ϕ_P (Fig. 3a) and as ϕ_P is changed at constant ϕ_S (Fig. 3b). Qualitative matching shows that we are capturing key attributes of the local chain correlations with this simple model. We allow ϵ to be a fit parameter that is constant regardless of the environment or molecular features. This matching with experiments enable parameterization, with $A_0 = 20.5, B_0 = 12.2, \text{ and } \tilde{\epsilon} = 0$. We use these values for all of the subsequent results.

3.4 Free energy of coacervation

We combine the expression for the free energy of interaction term (eqn (17)) with an entropic mixing contribution, and a phenomenological contribution to capture the excluded volume of all the non-water species:

$$\frac{\mathscr{F}}{Vk_{\rm B}T} = \frac{\phi_{\rm P}}{N} \ln \phi_{\rm P}/2 + \phi_{\rm S} \ln \phi_{\rm S}/2 + \phi_{\rm W} \ln \phi_{\rm W} - \frac{\phi_{\rm P}}{2} \ln \left[1 + A_0 \phi_{\rm S} + B_0 \phi_{\rm P} + e^{-\tilde{\epsilon}} + \sqrt{\left(1 + A_0 \phi_{\rm S} + B_0 \phi_{\rm P} + e^{-\tilde{\epsilon}}\right)^2 - 4\left(A_0 \phi_{\rm S} - B_0 \phi_{\rm P} + e^{-\tilde{\epsilon}}\right)} \right] + \kappa (\Lambda \phi_{\rm P} + \phi_{\rm S})^3$$
(19)

where $\tilde{\mu}_{s}^{0}$ and $\tilde{\mu}_{P}^{0}$ are reference chemical potentials and $A_{0} = \exp{\tilde{\mu}_{s}^{0}}$ and $B_{0} = \exp{\tilde{\mu}_{P}^{0}}$. This is an assumption that the environment surrounding the tagged polymer is near-ideal.²⁰ We conceptually justify this by observing that, in simulations of these dense Coulombic environments, correlations do not extend significantly beyond the immediate neighbors of the test molecule (which are included in the transfer matrix method).²⁵

We can demonstrate the suitability of this method by directly determining the adsorbed species along chains in coacervate simulations. We show our method schematically in Fig. 2. Along test chains, the nearest oppositely charged particle within a cutoff radius of $\tilde{r}_{\rm C} = 3$ around each monomer is assigned to each indexed bead. Assignments are unique, so that every neighboring particle is only used for a single monomer. This allows us to determine from simulation the sequence of 'adsorbed' species {*s_i*} which consists of C, P, P', and 0 designations. P and P' are defined such that an adsorbed monomer is considered

We have introduced a constant κ that parameterizes the strength of the excluded volume contribution. This term is third order to distinguish from the interaction term, which includes the two-body interactions (chain–salt and chain–chain interactions) that are represented by the interaction term. The constant $\Lambda = v_{e,P}/v_{e,S}$ accounts for the difference in excluded volumes v_e between the polymer *versus* salt species. The region of excluded volume around a salt ion is $v_{e,S} = 4\pi\sigma^3/3$, associated with the closest-approach distance of another species. This is different for the polymer, because the connectivity between the polymer beads forces overlap between their respective excluded volume regions. Polymer beads thus exclude less volume, and for excluded volume radius σ around beads that are connected with bonds separated by a distance σ , $\Lambda = 0.6875$. We discuss this term in more detail in Section 4.3.

The last two terms of eqn (19) correspond to the excess free energy $f_{\text{EXC}} = \mathscr{F}_{\text{EXC}}/V$, which is the portion of \mathscr{F} that does not



Fig. 3 Simulation (points) and theory (curves) describing the adsorption sequence statistics in various coacervate-forming systems at a number of values of ϕ_P and ϕ_S . (a) The conditional probabilities p(X|Y) of having a monomer with adsorbed state of type X immediately following a monomer with adsorbed state of type Y. p(C|C), p(C|Y), p(P'|P), and p(P'|P') as a function of salt concentration ϕ_S at constant $\phi_P = 0.06$. (b) The same conditional probabilities as a function of polymer concentration ϕ_P for constant $\phi_S = 0.06$. For both (a and b) there is near-quantitative fitting between theory and simulation, indicating that this formalism describes the environment surrounding a test chain.

include the configurational mixing entropy. This prediction can be tested by comparison to the values for $f_{\rm EXC}$ that are calculated from thermodynamic integration of simulations.⁵⁴ In Fig. 4, we plot free energy landscapes from both simulation and theory. These exhibit near-quantitative matching for $\kappa = 19.0$, except at high values of $\phi_{\rm P}$ and $\phi_{\rm S}$ that likely reflects the approximation of using a simple third-order term to describe excluded volume effects. We note that matching between simulation and theoretical $f_{\rm EXC}$ curves is aided by linear contributions that tilt the $f_{\rm EXC}$ landscape ($f_{\rm EXC} = f_{\rm EXC}^0 + M_1\phi_{\rm S} + M_2\phi_{\rm P}$, with constants M_1 and M_2). This has no impact on thermodynamic properties.

4 Coacervation predictions and comparison to simulation

To motivate a number of assumptions in the above derivation, we provided some comparison to simulation. In particular, we



Fig. 4 Excess free energy f_{EXC} calculated using the final two terms in eqn (19) (lines) and comparison with simulation values (points). (a) Constant ϕ_P curves as a function of ϕ_S and (b) constant ϕ_S curves as a function of ϕ_P . For (a and b), each curve is shifted vertically by a value $f_{EXC}^S = 0.25$ for visual clarity. We note that there is excellent quantitative agreement between all values of ϕ_P and ϕ_S .

demonstrated that the chosen form for the chemical potentials of the tagged polymer environment was motivated by comparing the adsorption sequence statistics. Furthermore, we were able to show that the $f_{\rm EXC}$ calculated from theory matched well with simulation calculations. We now demonstrate that the predictions of this theory are consistent with the current state of understanding of coacervation physics, including aspects that are not described by VO or related theoretical approaches.^{16,19,23,25}

4.1 Phase separation

Fig. 5a demonstrates a coacervation phase diagram, in the salt concentration *versus* polymer concentration plane. Consistent with previous observations of coacervate phase behavior,^{19,22,25} there is a two phase region at low $\phi_{\rm S}$ and $\phi_{\rm P}$ where the mixture will spontaneously phase separate into polymer-rich coacervate and polymer-dilute supernatant phases. We use the values of A_0 , B_0 , $\tilde{\epsilon}$, and κ determined previously, and we likewise include simulation results for the binodal curve on the same plot. We find that both results match nearly quantitatively. This is perhaps not entirely surprising, given the use of simulation to determine the fitting constants; however, we note that these constants are parameterized by molecular features rather than simply matching the phase diagram.



Fig. 5 (a) Phase diagram in the salt concentration $\phi_{\rm S}$ versus polymer concentration $\phi_{\rm P}$ plane calculated from both simulation and theory, with the binodal curves demarcating the two phase 2Φ region where coacervation occurs. Tie lines are drawn, denoting the equilibrium between the low- $\phi_{\rm S}$ coacervate phase (right branch of the binodal) and the high- $\phi_{\rm S}$ supernatant phase (left branch of the binodal). (b) Tie lines indicate a difference in salt partitioning between the coacervate (α) and supernatant (β) phases. We plot $\lambda = \phi_{\rm S}^{\alpha}/\phi_{\rm B}^{\beta}$ as a function of the supernatant salt concentration $\phi_{\rm B}^{\beta}$. For all $\phi_{\rm S}^{\beta}$, $\lambda < 1$ indicating that salt is depleted from the coacervate phase.

One important feature of this prediction is the slope of the tie lines that connect the coexisting supernatant and coacervate phases. In most coacervate theories, these are non-horizontal to reflect the uneven partitioning of salt into the two phases.¹⁹ Voorn-Overbeek predicts an excess of salt in the coacervate phase, leading to a positively-sloped tie line.^{19,24,26} However, recent simulation and theory work by the authors, ^{23,25,54} in line with experimental results,²⁵ demonstrates that the tie line will typically have a negative slope. The physical motivation for this negative slope is that the high polymer density in the coacervate phase excludes the volume accessible to the salt, which will subsequently prefer to be in the polymer-dilute supernatant phase. Our theory predicts this behavior, and we quantify the extent of this partitioning by plotting in Fig. 5b the ratio of the salt concentration between the two phase, $\lambda = \phi_{\rm S}^{\alpha}/\phi_{\rm S}^{\beta}$, where α denotes the coacervate phase and β denotes the supernatant phase. In Fig. 5, quantity λ is plotted versus $\phi_{\rm s}^{\beta}$, and is always $\lambda < 1$ indicating that salt preferentially partitions to the supernatant phase. Simulation and theory agree qualitatively, and are consistent with previous simulation and experimental results.^{23,25}

4.2 Counterion release and chain-chain interactions

We can quantify how this phase separation is related to the mechanism of counterion release, one of the traditional concepts of coacervation. The average fraction of monomers with a condensed salt ion $\langle \theta_{\rm C} \rangle$ can be calculated from the partition function eqn (16):

$$\langle \theta_{\rm C} \rangle = k_{\rm B} T \left(\frac{\partial \ln \xi}{\partial \mu_{\rm S}} \right) = \frac{A_0 \phi_{\rm S}}{2\xi} \\ \times \left[1 + \frac{A_0 \phi_{\rm S} + B_0 \phi_{\rm P} + e^{-\tilde{\epsilon}} - 3}{\sqrt{(A_0 \phi_{\rm S} + B_0 \phi_{\rm P} + e^{-\tilde{\epsilon}} + 1)^2 - 4(A_0 \phi_{\rm S} - B_0 \phi_{\rm P} + e^{-\tilde{\epsilon}})}} \right]$$

$$(20)$$

This is a function of salt and polymer concentration, and is plotted alongside simulation values in Fig. 6 as a function of polymer concentration $\phi_{\rm P}$ (Fig. 6a) and $\phi_{\rm S}$ (Fig. 6b). Indeed, at low $\phi_{\rm P}$ there are significantly more adsorbed counterions, which monotonically decreases with $\phi_{\rm P}$. This is indicative of a counterion condensation and release effect. Increased salt concentration $\phi_{\rm S}$ leads to a monotonic increase of $\langle \theta_{\rm C} \rangle$ due to the prevalence of salt ions.

The entropic driving force for coacervation is only partly driven by counterion release. There is another entropic driving force due to the increasing number of interactions between the polymers. We also plot this in Fig. 6, by calculating the average number of new polymers P' per chain $\langle \theta_{P'} \rangle$:

$$\langle \theta_{\mathbf{P}'} \rangle = k_{\mathbf{B}} T \left(\frac{\partial \ln \xi}{\partial \mu_{\mathbf{P}}} \right) = \frac{B_0 \phi_{\mathbf{P}}}{2\xi}$$

$$\times \left[1 + \frac{A_0 \phi_{\mathbf{S}} + B_0 \phi_{\mathbf{P}} + \mathrm{e}^{-\tilde{e}} + 3}{\sqrt{(A_0 \phi_{\mathbf{S}} + B_0 \phi_{\mathbf{P}} + \mathrm{e}^{-\tilde{e}} + 1)^2 - 4(A_0 \phi_{\mathbf{S}} - B_0 \phi_{\mathbf{P}} + \mathrm{e}^{-\tilde{e}})}} \right]$$
(21)

The monotonic increase in the quantity $\theta_{P'}$ with ϕ_{P} is due to the increasing abundance of options for polymer–polymer interactions, which is entropically favorable. This is one way in which coacervation is different from the behavior of isolated pair complexes. Pair complexes occur in the dilute limit where two oppositely-charged polyelectrolytes interact *via* the counterion release mechanism; however, these polyelectrolytes only have the option of interacting each other over the entire length of their respective chain contours. As concentration increases, there is an entropic benefit of each polyelectrolyte interacting with more than one chain. A similar effect is found in physical gelation,⁵⁶ polymer solution phase behavior,⁵⁷ and dense polyelectrolytes;⁵⁸ in all of these examples there is a strong entropic contribution to the free energy due to the number of possible interactions.

4.3 Charge density effects

Previous work by the authors has demonstrated the importance of local charge density, with drastic reductions in the two-phase coexistence region as the spacing between charges is increased.^{23,25} We consider two molecular effects that contribute to charge spacing, which can be incorporated directly into this formalism.



Fig. 6 Fraction of monomers with 'adsorbed' species *i*, $\langle \theta_i \rangle$, as a function of (a) ϕ_P (at constant $\phi_S = 0.09$) and (b) ϕ_S (at constant $\phi_P = 0.09$). $\langle \theta_C \rangle$ is a measure of the number of condensed counterions, and monotonically decreases as the concentration of polymer ϕ_P is increased. This reflects the traditional counterion release driving force for coacervation. The amount of condensed counterions increases with ϕ_S , reflecting the increased abundance of salt ions. The number of new polymer interactions per monomer, $\langle \theta_{P'} \rangle$, monotonically increases as the concentration of polymer ϕ_P is increased. This is a further driving force for coacervation, due to the increased entropy of having a large number of combinations of possible polymer–polymer interactions.

We first consider the entropy of adsorbing subsequent monomers, which affects the factor *E*. We postulate a form $E = \Delta^{-2}$ where Δ is the normalized spacing between adjacent charges. This scaling is related to the entropic penalty of confining a single monomer along a run of monomers, which would

otherwise sweep the surface of a sphere $\sim \Delta^2$ but instead must be nearby the chain (see schematic in Fig. 7a). Thus, as spacing increases, the entropic penalty to adsorb a monomer (after placing the initial monomer) becomes more significant due to the larger area that the monomer can sweep out in our RPM-based model.



Fig. 7 (a) As the spacing Δ between charges increases, then the entropic penalty for continued adsorption of monomers increases; this is due to the larger angle swept by a non-adsorbed charge, which corresponds to a larger phase space. (b) The sequence probability p(P|P) as a function of Δ and ϕ_P (constant $\phi_S = 0.06$). Theory that accounts for the entropic penalty for chain adsorption captures the trend in simulation describing the local environment around a test chain. (c) Spacing affects the volume excluded by the charged species. An isolated salt ion excludes a volume within a diameter of the particle (light red circle). In a chain, the polyelectrolyte charges exclude a smaller volume (light orange circle), which is a function of Δ . (d) Phase diagrams from both simulation and theory, including different values of Δ . The combined contribution of chain adsorption entropy and excluded volume leads to a marked decrease in the coexistence region, which is qualitatively demonstrated in both simulation (unconnected, lighter symbols) and theory (connected, bold symbols).

We demonstrate that this effect captures the local structure in simulation. Fig. 7b shows the calculation of the quantity $p(\mathbf{P}|\mathbf{P}) = E/(A + B + D + E) = \Delta^{-2}/(A_0\phi_{\rm S} + B_0\omega_A\phi_{\rm P}/\omega_1 + v_1\mathrm{e}^{-\tilde{e}}/v_A + \Delta^{-2})$ plotted alongside simulation calculations of the same quantities from the adsorption sequence for a number of charge spacings Δ and volume fractions $\phi_{\rm P}$. Without changing the parameters A_0 , B_0 , or \tilde{e} , we can fit the entire set of curves.

Charge spacing further impacts the excluded volume associated with the polymer. The proximity of neighboring polymer beads decreases the effective excluded volume, because they jointly occupy regions that would otherwise separately prevent the approach of salt ions (see schematic in Fig. 7c). This was previously captured by $\Lambda = v_{e,P}/v_{e,S}$, which we can write as a function of bead spacing along the polymer. A single salt bead occupies a volume $v_{e,S} = 4\pi\sigma^3/3$. For a polymer, half of the overlap volume must be subtracted because it is shared between any pair of adjacent beads; however, this is multiplied by two adjacent beads. This leads to the result $v_{e,P} = 4\pi\sigma^3/3 - \frac{\pi}{12}(4\sigma + \Delta\sigma)(2\sigma - \Delta\sigma)^2$, providing an expression for Λ :

$$\Lambda = 1 - \frac{(4+\Delta)(2-\Delta)^2}{16}$$
(22)

We demonstrate the combined strength of these effects by calculating the phase behavior for a series of polymer $\Delta = 1.0-1.2$ in Fig. 7d for both simulation and theory. We observe the expected decrease in the coexistence region as the charge spacing is increased, which is qualitatively consistent between simulation and theory. We note that matching becomes less quantitative as Δ is increased, which represents a limitation of this model. The increase in charge spacing moves the system away from a high charge-density limit, where charged interactions are highly screened and neighboring 'adsorbed' molecules drive the thermodynamics. As Δ increases and charge density is decreased, long-range correlations become more important and field theoretic methods become increasingly appropriate.^{24,29-33}

4.4 Electrostatic strength

One surprising result of this theory is that eqn (19) is not explicitly dependent on the strength of the electrostatic interactions (*via* the Bjerrum length $\lambda_{\rm B} = e^2/(4\pi\varepsilon_{\rm r}\varepsilon_0 k_{\rm B}T)$). This stems from the high charge-density limit considered in this work, where nearly all charges are effectively 'paired' in our framework. Within this limit, we can demonstrate that λ_B does not play a role. We do this by changing the relative dielectric constant ε_r from ε_r = 78.5 to ε_r = 60, which increases the strength of the Coulomb interaction by ca. 31%. The simulation results are plotted in Fig. 8a, which show essentially no difference in the phase behavior, despite the considerable change in the strength of the Coulomb interaction. Similarly, the test chain neighbor conditional probabilities p(X|Y) match between the different values of ε_r , and are shown in Fig. 8b. These results are consistent with experimental observation that coacervation is primarily an entropic process, with calorimetry consistently showing only small enthalpic changes during coacervate formation.40,59

4.5 Non-stoichiometric coacervation phase diagrams

Most existing coacervate theory considers stoichiometric mixtures of polycation and polyanion, where there is equal number of polycation charges and polyanion charges,¹⁶ with a few exceptions.^{37,60,61} We can extend this theory to capture the phase behavior as an excess of polycation or polyanion charges is present in the system. This involves changing the interaction free energy to be rewritten with explicit reference to the polyelectrolyte species of interest:

$$\begin{aligned} \frac{\mathscr{F}_{\text{int},\pm}}{Vk_{\text{B}}T} &= \\ &-\frac{\phi_{\text{P}\pm}}{2} \ln \left[1 + 2A_0 \phi_{\text{S}\mp} + 2B_0 \phi_{\text{P}\mp} + e^{-\tilde{\epsilon}} \right. \\ &+ \sqrt{\left(1 + 2A_0 \phi_{\text{S}\mp} + 2B_0 \phi_{\text{P}\mp} + e^{-\tilde{\epsilon}} \right)^2 - 4 \left(2A_0 \phi_{\text{S}\mp} - 2B_0 \phi_{\text{P}\mp} + e^{-\tilde{\epsilon}} \right)} \right] \end{aligned}$$

$$(23)$$



Fig. 8 (a) Phase diagram for both $\varepsilon_r = 78.5$ (black points) and $\varepsilon_r = 60.0$ (red points), along with theory (black line). We note that both phase diagrams are almost exactly the same, despite electrostatic interactions being 31% stronger for the red points. This is predicted by our theory, which does not have a dependence on ε_r except in the assumption that we are at the high charge-density limit. (b) Example test chain probabilities p(X|Y) for both $\varepsilon_r = 78.5$ (circles) and $\varepsilon_r = 60$ (triangles). These representative results demonstrate that a test chain experiences the same environment regardless of the strength of the electrostatic interactions, in this limit of high charge-density.



Fig. 9 Three-dimensional phase diagram showing phase behavior as the concentration of polycation (ϕ_{P+}) and polyanion (ϕ_{P-}) are varied independently. ϕ_{S}^* is the concentration of excess salt, beyond the excess cations or anions required to balance the charges on the polyelectrolytes. All plots are the same, only from different angles. Deviations from the $\phi_{P+} = \phi_{P-}$ line quickly decrease the coexistence region. Points are calculated phase coexistences connected by tie lines, which show a decrease in salt concentration ϕ_{S}^* in the coacervate phase as compared to the supernatant phase, consistent with the two-dimensional phase diagram in Fig. 5a. The far left plot demonstrates that these tie lines move away from the $\phi_{P+} = \phi_{P-}$ line as they move toward the coacervate phase, demonstrating that the coacervate phase accommodates more disparity in the polyelectrolyte stoichiometry than the supernatant phase.

We note that the prefactor includes the volume fraction of the test polymers, while the natural log term is concerned with the concentrations of the surrounding oppositely-charged species. The final free energy is therefore:

$$\frac{\mathscr{F}}{Vk_{\mathrm{B}}T} = \frac{\phi_{\mathrm{P}+}}{N_{\mathrm{P}+}} \ln \phi_{\mathrm{P}+} + \frac{\phi_{\mathrm{P}-}}{N_{\mathrm{P}-}} \ln \phi_{\mathrm{P}-} + \phi_{\mathrm{S}+} \ln \phi_{\mathrm{S}+} + \phi_{\mathrm{S}-} \ln \phi_{\mathrm{S}-}$$
$$+ \phi_{\mathrm{W}} \ln \phi_{\mathrm{W}} + \frac{\mathscr{F}_{\mathrm{int},+}}{Vk_{\mathrm{B}}T} + \frac{\mathscr{F}_{\mathrm{int},-}}{Vk_{\mathrm{B}}T} + \kappa (\Lambda \phi_{\mathrm{P}} + \phi_{\mathrm{S}})^{3}$$
(24)

We plot the results of this calculation in Fig. 9 on a plot of ϕ_{S}^{*} versus $\phi_{P^{+}}$ and $\phi_{P^{-}}$. The asterisk on ϕ_{S}^{*} denotes that this is the salt added beyond the counterions that are needed to make up the difference between ϕ_{P+} and ϕ_{P-} . We obtain results that are consistent with the previous literature,¹ with a region around $\phi_{\rm P+} \approx \phi_{\rm P-}$ that phase separates and shrinks as salt is added. In Fig. 9, the points shown forming the surface in the $\phi_{\rm S}^0 - \phi_{\rm P+} - \phi_{\rm P-}$ space represent individual calculations of phases in equilibrium, separated by tie lines. Similar to results in Fig. 5, the downward slope of the tie lines denotes that salt preferentially partitions to the supernatant phase. However, in off-stoichiometric mixtures the coacervate phase accommodates more of the un-matched polyelectrolyte, as indicated by the tie lines moving away from $\phi_{P+} = \phi_{P-}$ as they move toward the coacervate phase. This preference for the unmatched polyelectrolyte and its counterions to partition into the coacervate phase is unsurprising; the excess counterions will be condensed to the unmatched polyelectrolyte in the supernatant phase, which is entropically unfavorable compared to the coacervate phase where the counterions will no longer be condensed.

5 Conclusion

Here we presented a theory for complex coacervation that incorporates molecular aspects that are known to be crucial to understanding the thermodynamics of these materials. Specifically, we base this model on counterion condensation and release concepts^{26,35,36,39,59} in order to capture the effect of local correlations due to the connected polyelectrolyte charges.²³ The results of this model are compared to the local environment around a test chain as determined in simulation, demonstrating that the assumptions that we make are appropriate for the salt and polymer concentration regimes relevant to complex coacervation.^{22,28} We see near-quantitative agreement between the results of this theory and the phase behavior of complex coacervates in simulation, including features such as the behavior of the tie lines and the influence of charge density on coacervation.

We note that this model relies on the short range of correlations due to high charge density. This allowed us to use simplistic arguments for the values of $\mu_{\rm P}$ and $\mu_{\rm S}$, and an assumption that longer-range correlations are able to be neglected at distances further along the polyelectrolyte chain. For the latter assumption, the current transfer matrix model only accounts for monomers that are immediately adjacent along the chain. This may not be adequate in dilute systems where the electrostatic correlations will cause an adsorbed counterion/ chain at monomer *i* to strongly affect nonadjacent monomers |j - i| > 1. We speculate that some combination of this model with standard field theoretic approaches^{24,29–31,33} may be useful to capture these long-ranged correlations in the dilute regime.

The advantage of this model is that it considers local connectivity-based correlations, such as the local alignment of oppositely-charged chains, in a fashion that is analytically tractable and motivated by structure known from molecular simulation. The excess free energy expression f_{EXC} can be used as an input for more complicated theoretical arguments, such as those for coacervate-driven self-assemblies; indeed, this is the limiting aspect of most current models for coacervate-driven assembly,^{9,33} which either use field theory results⁹ or full molecular simulation⁵⁴ to determine the local effect of electrostatic attractions and correlations.

Conflicts of interest

There are no conflicts of interest to declare.

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